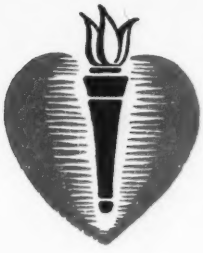
OCTOBER 1957
VOL. XVI NO. 4

Circulation

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION



30th Scientific Sessions of the American Heart Association
Commemorating the Tercentenary of William Harvey
Chicago, Ill., from October 25–28, 1957

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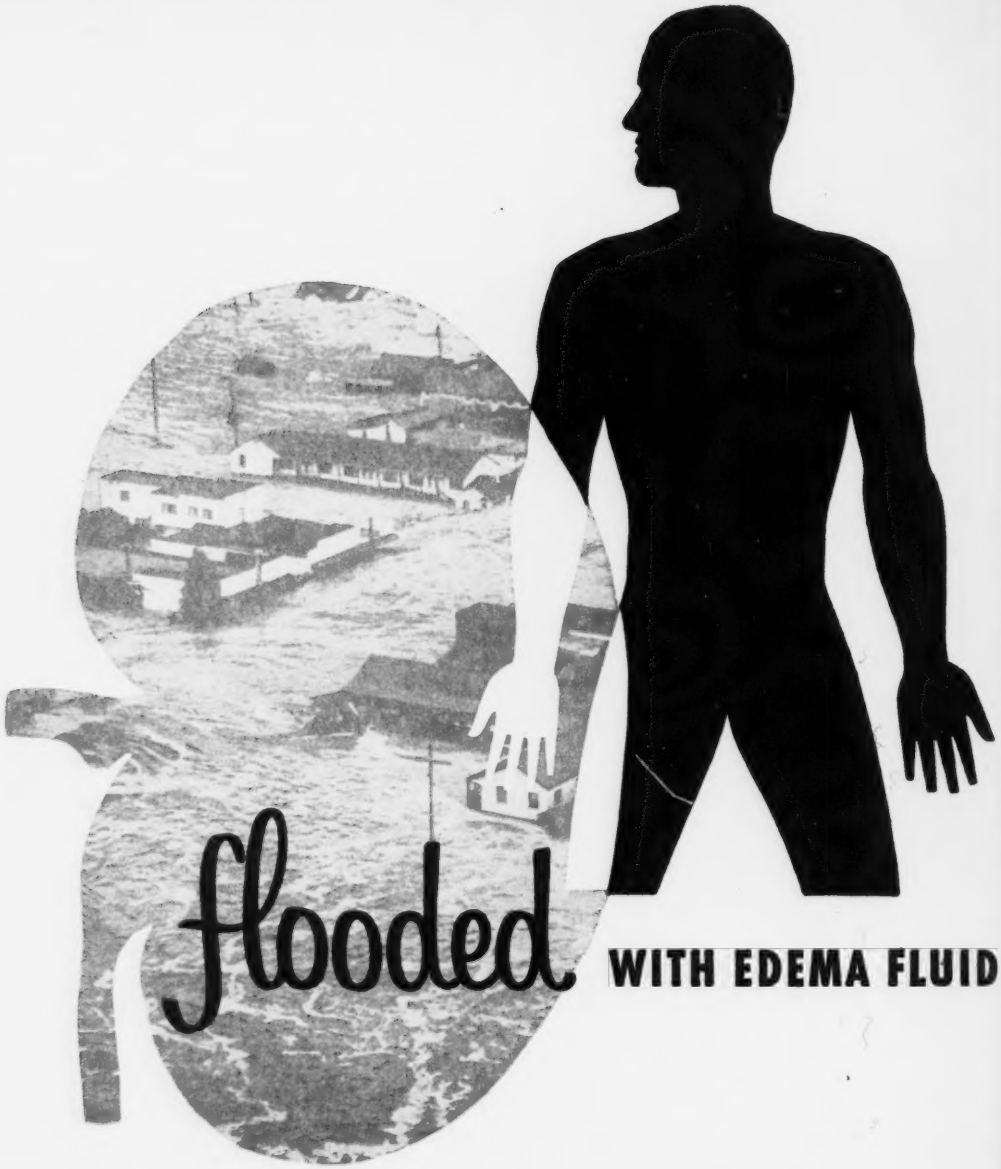

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Editorial

Cardiology Divided

NOT more than 20 years ago, cardiology was exclusively a branch of internal medicine. As such, it relied on the general tools and methods accessible to clinical medicine of that period. Diseases of the heart were classified, their symptoms were catalogued, and their natural history was described. These efforts have borne valuable fruit: the signs and symptoms of coronary thrombosis have been described, the natural history of rheumatic heart disease has been outlined, and congenital diseases of the heart were classified. During this phase investigations on the heart and circulation, not directly connected with clinical facts, were carried out primarily in the physiologic laboratory. There was occasional cooperation between the physiologists and the clinical cardiologists. In the main, however, investigative efforts of the clinicians were directed toward exploiting a new tool, the electrocardiogram, and toward establishing its validity as a diagnostic aid.

The second phase began with the development of new tools and technics. The study of circulatory dynamics emerged from the physiologic laboratory and invaded the medical and even the surgical wards. Catheterization of the heart, angiocardiography, electrokymography, and ballistocardiography became instruments around which "cardio-respiratory" laboratories were formed in almost all teaching hospitals in the nation. In the beginning of this era, only 15 years ago, this was a virgin field. The progress since then has been so rapid, that scientific personnel to head and staff these laboratories has become scarce, and untrained clinicians are often recruited to fill the breach that should be occupied by physicians carefully trained in the physiologic technics. The rapid rise in the interest in circulatory dynamics is no coincidence. Catheterization of the heart and angiocardiography and, to a lesser extent, ballistocardiography and electrokymography, have become diagnostic tools. For better or for worse, they have become essential in the diagnosis of congenital heart disease, and left-heart catheterization promises to be of value in recognition and evaluation of lesions in the left side of the heart. Despite the overwhelming use of these technics for diagnostic purposes, their importance for physiologic studies on the circulation has not come to an end. Undoubtedly there is still much room for well trained and resourceful workers, as long as the technics are not used only as handmaidens of the clinician.

Within recent years cardiologists have come to the realization that in addition to the clinical cardiologist and the clinical investigator, workers in the fundamental sciences of biochemistry and biophysics can make considerable contributions to their discipline. Enzyme chemistry and biochemistry on a molecular level have furnished technics and, more important, ideas for the investigation of heart failure, myocardial anoxia, and myocardial metabolism in general. Energy production of the heart has been studied in tissue slices, or homogenates of normal and abnormal heart muscle, and in the whole heart in vitro and in vivo. Energy utilization of the heart has been

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investigated by a study of the contractile proteins of the heart muscle. These investigations have led to important findings: i. e., that the human heart utilizes primarily noncarbohydrate substrates; that myocardial failure seems to be the result of changes in contractile proteins; and that ischemia of heart muscle may lead to prolonged and reversible glycolytic changes in the myocardial metabolism.

It is clear that no one individual possesses either the training or the technics available to master all 3 divisions of cardiology. As a result, workers in these divisions, as in the building of the tower of Babel, speak in different tongues and do not comprehend the aims of their fellow workers. There is the clinical cardiologist, interested in the physical signs of heart disease and usually well informed on electrocardiography and vectorcardiography. His is usually the responsibility for patient care. There is the clinical physiologist, who emphasizes dynamic alterations without much regard for physical signs, history, or treatment. And finally, there is the biochemist or biophysicist whose pursuits are even more academic and more remote.

A divergence of interests is as it should be. Without it individual progress is not possible. A lack of mutual understanding, however, is not conducive to medical progress. This does not imply that there should be centralization of all clinical and scientific labors. A cardiologist with a purely clinical orientation makes a poor director of a laboratory concerned with circulatory and biochemical studies, and a biochemist or physiologist is not likely to show much clinical judgment. How, then, can we avoid the growing schism of physicians and scientists interested in diseases of the heart?

The solution may well lie in the training of physicians interested in cardiology. Without falling into the pitfall of trying to learn everything and ending by knowing nothing, a young physician interested in cardiology should undergo clinical, physical, biochemical and biophysical training. One of these should later be his major pursuit according to his ability and inclination. But he should be made aware of the others through personal contact and through proximity in space. The space factor is often neglected, either through lack of facilities or, more often, through lack of understanding. Frequently one finds that the heart station, concerned with reading and mounting of electrocardiograms and the study of vectorcardiography, is far removed from the catheterization laboratory; this in turn often contains only the fluoroscope and some accessories, while the laboratory for gas analysis is housed either in a routine hospital laboratory or in a department of physiology. Finally, work on fundamental biochemical problems related to the heart is often being pursued across the street in a department of biochemistry. Whenever space permits, these units should be housed in close proximity.

The advance in clinical and fundamental cardiology within the last 10 years has been spectacular. Diversion and specialization have been the price. Efforts should now be made to bring individual branches of a great discipline back under one roof, both in an intellectual and a physical sense.

RICHARD J. BING

These things then are as it were the parts, and the footsteps of the passage, and Circulation of the blood; to wit, from the right ear into the ventricle, out of the ventricle through the lungs into the left ear, then into the left ventricle, into the aorta, and into all the arteries from the heart, by the porosities of the parts into the veins, and by the veins into the Basis of the heart, the blood returns most speedily.—WILLIAM HARVEY *De Circulatione Sanguinis*, 1649.

Effects of Serotonin Antagonists in Normal Subjects and Patients with Carcinoid Tumors

By ROLAND SCHNECKLOTH, M.D., IRVINE H. PAGE, M.D., F. DEL GRECO, M.D., AND A. C. CORCORAN, M.D.

The pathogenesis of flushing attacks in patients with malignant carcinoid tumors is attributed to the direct pharmacologic effect of excessive amounts of circulating serotonin. It was hoped that potent serotonin antagonists might relieve symptoms of the carcinoid syndrome in the inoperable patient. The nature of flushing attacks was studied in carcinoid patients and the influence thereon of 3 serotonin antagonists, a benzyl analog of serotonin, bromo-lysergic acid diethylamide, and chlorpromazine. The systemic, subjective, and vascular effects of these antagonists in normal subjects were also investigated.

AFTER the isolation, determination of structure,[1-5] and synthesis[6] of serotonin (5-hydroxytryptamine), Erspamer and Asero[7] found that the substance producing the fluorescence and staining properties of the chromaffin cells of the intestinal tract was identical with serotonin. Serotonin is formed by enzymatic hydroxylation and decarboxylation of the amino acid, tryptophan, and is degraded in part to 5-hydroxyindoleacetic acid, which is excreted into the urine.[8]

Malignant gastrointestinal carcinoid tumors, which are believed to be derived from chromaffin cells, may produce excessive amounts of serotonin.[9] When enough functioning tumor tissue is present, usually because of hepatic metastases, a syndrome ensues consisting of diarrhea, right-sided valvular heart disease, cyanosis, and an unusual flushing of the skin.[10-13] Increased amounts of serotonin are found in the blood of these patients[14] and large amounts of 5-hydroxyindoleacetic acid may appear in the urine,[15] indicating that this is an endocrine tumor, as was suspected in 1914 by Masson.[16]

The pathogenesis of the cutaneous vascular changes has not been established although they have been attributed to the direct pharmacologic effect of excessive amounts of circulating serotonin liberated from the tumor. The endocardial sclerotic lesions have been ascribed to a direct action of serotonin;[12] destruction in the lungs of serotonin released from liver metastases might account for the failure to find lesions in the left heart. Since elevation of the pulmonary artery pressure may follow the injection of serotonin into dogs[17] or normotensive and hypertensive patients,[18] Thorson[19] suggested that the profound hemodynamic changes associated with attacks of flushing might place an increased strain on the right heart and could be a basis for the development of valvular lesions.

A serotonin antagonist, 1-benzyl-2,5-dimethyl serotonin hydrochloride, abbreviated BAS, a benzyl analog of serotonin (fig. 1) was synthesized by Woolley and Shaw.[20, 21] Orally administered in doses of 1 mg. per Kg., it protected dogs from the pressor action of intravenous serotonin.[22] Another serotonin antimetabolite, 2-bromo-d-lysergic acid diethylamide, hereinafter called bromo-LSD (coded as BOL 148) (fig. 1), was highly effective in blocking the action of serotonin on isolated uterine and intestinal strips;[23, 24] inhibition of the effects of serotonin on arterial pressure and renal function was also shown in vivo in the intact anesthetized rat.[25] A third substance, chlorpromazine hydrochloride, bears no structural resemblance to serotonin, but it has also been shown to antagonize the effects of serotonin in vitro.[26-28] It seemed to us that these potent serotonin antagonists might relieve the symptoms of the carcinoid syndrome.

The present study is based on observations

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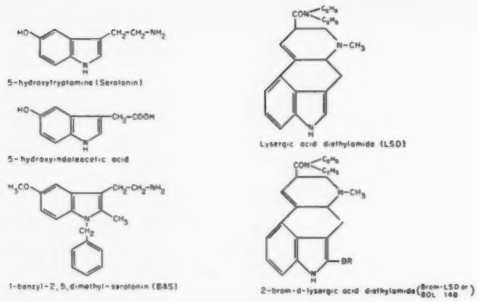

FIG. 1. Chemical structures of serotonin, 5-hydroxyindoleacetic acid, and antimetabolites of serotonin (BAS, LSD, and bromo-LSD).

in 5 normal subjects and in 2 patients with malignant carcinoid tumors of the intestinal tract. Neither of the latter patients had clinical evidence of associated endocardial or valvular heart lesions. Both, however, had frequent attacks of flushing. These enabled us to study (1) the nature of this flushing, (2) the influence thereon of 3 serotonin antagonists, BAS, bromo-LSD, and chlorpromazine, and (3) the effects of these antagonists on the vascular action of endogenous and exogenous serotonin, as well as (4) other systemic and subjective effects of these agents.

METHODS

The effects of intravenous administration of norepinephrine, sodium nitroprusside, serotonin creatinine sulfate, and tetraethylammonium chloride on the arterial pressure of 1 carcinoid patient (case 1) were directly measured by means of a Statham pressure transducer (P-10D) connected to an inelastic polyethylene catheter inserted into a brachial artery, and the pressure changes inscribed on a Brush recorder. The patient was kept supine and without sedatives.

Cardiac catheterization was performed in 1 carcinoid patient (case 1) by Drs. F. Mason Sones and Jean Mignault of the Division of Medicine. After resting arterial and intracardiac pressures were recorded and blood withdrawn for oxygen and serum serotonin* determinations, an intravenous infusion of bromo-LSD (1.0 mg. per minute) was started and determinations repeated after 10 minutes of infusion.

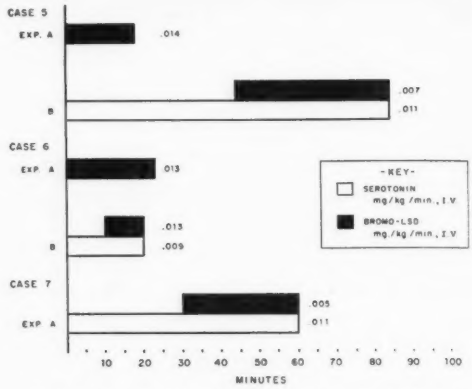

FIG. 2. Psychological effects of bromo-LSD were studied in normal subjects (cases 5, 6, and 7) during intravenous infusions of bromo-LSD alone or during simultaneous infusions of serotonin.

The effects of bromo-LSD on mental function and on the vascular action of serotonin were studied in both carcinoid patients (cases 1 and 2) and in 3 normal subjects (cases 3, 4, and 5). Arterial pressure was measured continuously. Single intravenous injections of 2 to 4 mg. of serotonin creatinine sulfate or 10 μg. of norepinephrine were administered before and during intravenous infusions of bromo-LSD; the latter was given at rates ranging from 0.5 to 5.0 mg. per minute, and in total doses of from 15 to 160 mg.

The psychic effects of bromo-LSD were further studied in 3 normal subjects (cases 5, 6, and 7) (fig. 2). A constant intravenous infusion of bromo-LSD was administered to cases 5 and 6, at rates of 0.014 mg. per Kg. per minute and 0.013 mg. per Kg. per minute to total doses of 18 mg. and 22 mg., respectively. The infusion of bromo-LSD was repeated on a subsequent day in cases 5, 6, and in case 7, but on this occasion was preceded for 10 to 44 minutes by a constant intravenous infusion of serotonin creatinine sulfate, at rates of 0.011 mg. per Kg. per minute, 0.009 mg. per Kg. per minute, and 0.011 mg. per Kg. per minute, to total doses of 66 mg., 13 mg., and 31 mg. of serotonin, respectively. An infusion of bromo-LSD was then started in another vein and continued simultaneously with the serotonin for 10 to 40 minutes.

The daily urinary excretion of 5-hydroxyindoleacetic acid was measured by the method of Udenfriend, Titus, and Weissbach.[29]

CASE REPORTS

Case 1. W. J. C., a 29-year-old man, was hospitalized in the Seattle Veterans Administration Hospital in January 1955, with complaints of chronic diarrhea and paroxysmal attacks of flushing of the skin of approximately 3 years' duration. The results

* These analyses were kindly performed by Dr. Sidney Udenfriend, Laboratory of Chemical Pharmacology, National Heart Institute, National Institutes of Health, Bethesda, Md.

of extensive studies made at that time were reported elsewhere.[30] At laparotomy on February 5, 1955, a firm inoperable mass was found at the pylorus with extension to regional lymph nodes; the liver was enlarged by multiple nodular metastases. The microscopic diagnosis by liver biopsy was malignant carcinoid, secondary in the liver. A postoperative episode of hallucinations and delirium cleared spontaneously after 2 days. Abdominal cramps lessened after discharge, but attacks of flushing continued.

He was referred to us for further study by Dr. D. E. Nolan, Veterans Administration Hospital, Seattle, Washington, on April 15, 1956. Cutaneous changes consisted in persistent cyanosis of the face and paroxysmal attacks of intense purple-red flushing of the face, neck, and extremities. With the latter there were often associated sensations of local heat in the face and generalized tingling of the skin. Palpitation, tachycardia, breathlessness, and sweating were common during the attacks. Episodes of flushing lasted 2 to 3 minutes, occurred spontaneously 10 to 20 times a day, and were often accompanied by abdominal cramps and nausea. Flushes could also be provoked by emotional stress, physical exertion, or evacuation of the bowels, and were aggravated by standing.

The pulse was 80 and the blood pressure 112/72 mm. Hg lying and 100/70 mm. Hg standing. The sclerae were slightly icteric; and optic fundi were normal. The heart was not enlarged, rhythm was regular, and there was a soft murmur at the apex. No clubbing of the digits was seen; peripheral arterial pulsations were normal. The liver was firm, nodular, nontender, and palpable 6 cm. below the costal margin.

Roentgenograms showed the heart to be normal in size and configuration; cardiac pulsation appeared normal during fluoroscopy. An electrocardiogram showed sinus rhythm, slight elevation of the S-T segment in leads I, II, aV_L, V_{2-6}, and slight depression in Lead aV_R.

Hemoglobin was 16 Gm. per cent; hematocrit, 58 ml.; red blood count, 6.48 million per $mm.^3$ with occasional target cells; white blood count, 8,800 per $mm.^3$; the differential count was normal. The platelet count, bleeding time, coagulation time, clot retraction, prothrombin time, sedimentation rate, icterus index, thymol turbidity, fasting blood sugar, blood urea, and plasma creatinine were normal. The electrophoretic pattern of the serum proteins and the ultracentrifuge lipoprotein pattern were also normal.

The total blood histamine was 11 μg. per cent, which is only slightly higher than usual values (4 to 7 μg. per cent).* The urine histamine was 27 μg. and the urine histidine 120 mg. per 24 hours; both values were considered to be within normal limits.

The daily urinary excretion of 5-hydroxyindoleacetic acid averaged 239 mg. per 24 hours and ranged from 174 to 292 mg. per 24 hours (normal range, 2 to 9 mg. per 24 hours).

Case 2. Repeated attacks of vomiting with abdominal cramps and distention began in 1951 in L. C. B., a 61-year-old woman. Three months later, laparotomy revealed a small malignant carcinoid tumor partially obstructing the jejunum; the tumor had invaded the peritoneum and pelvic organs and could not be removed. Clinical improvement followed an enteroenteroanastomosis, but attacks of partial bowel obstruction recurred every 3 to 4 months. In 1955 she became aware of mild to intense red flushing of her face and upper chest 1 to 10 times daily, occurring spontaneously but aggravated by eating or by emotion. Palpitations, headache, and tachycardia accompanied the attacks. Arterial pressure was 130/80 mm. Hg; physical and laboratory examinations gave no evidence for any cardiac lesion. The daily urinary excretion of 5-hydroxyindoleacetic acid averaged 25 mg. per 24 hours (range 14 to 44 mg. per 24 hours).

Results

Studies on Flushing Phenomenon

Histamine phosphate (0.025 mg.) administered intravenously, acetyl-β-methylcholine chloride (15 mg.) or epinephrine (0.25 mg.) given by subcutaneous injection, or alcohol (60 ml.) by mouth did not provoke a typical flush in either carcinoid patient. Atropine sulfate (1.2 mg.) or tetraethylammonium chloride (TEAC) (10 mg. per Kg.) administered intravenously did not prevent spontaneous flushing attacks.

In case 1, in contrast with the effect of epinephrine, the intravenous injection of 10 μg. of norepinephrine produced an intense flush, identical with that of spontaneous attacks; the flush appeared during the depressor phase of 10 to 20 mm. Hg that followed the initial abrupt rise in pressure (fig. 3). Repetitive injection of norepinephrine induced generalized flushing that subsided usually before the blood pressure returned from its depressed to control levels. In the same patient, lowering the blood pressure from 110/72 to 90/60 mm. Hg by intravenous infusion of sodium nitroprusside (100 μg. per ml.) also induced a typical flush; a further decrease of arterial pressure to 80/50 mm. Hg intensified the flush. Intravenous injection of 3

* These analyses were kindly performed by Dr. Brian Rose, University Clinic, Royal Victoria Hospital, Montreal, Quebec, Canada.

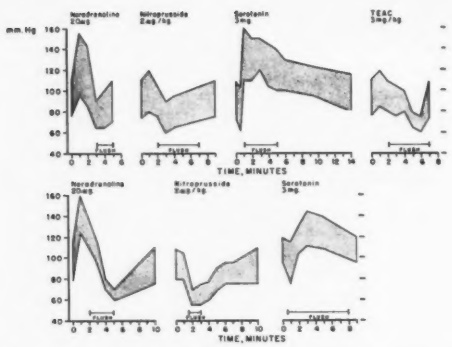

FIG. 3. Flushing in a carcinoid patient (case 1) associated with alterations of arterial pressure due to norepinephrine, sodium nitroprusside, and serotonin before and after TEAC.

mg. of serotonin creatinine sulfate was followed by a marked pressor response and an intense flush. Repeated doses of TEAC were then injected intravenously for a total dosage of 10 mg. per Kg.; after each injection a mild flush appeared with every fall in arterial pressure. After TEAC, the pressor response to norepinephrine was slightly enhanced and the pressor response to serotonin reduced, but the flushes induced by these drugs or by nitroprusside were neither prevented nor intensified.

Effect of Serotonin Antagonists

Oral Administration of BAS. BAS was given to case 1 by mouth in gradually increasing doses of 100 to 400 mg. (1.8 to 7.5 mg. per Kg.) for 9 days. The drug had no effect on blood pressure and pulse rate, and the number of flushes was the same. The patient thought, however, that their severity was slightly diminished. The daily urinary excretion of 5-hydroxyindoleacetic acid was not affected.

Oral Administration of Bromo-LSD. Bromo-LSD was given to case 2 by mouth in increasing doses up to 20 mg. daily for 7 days. The patient noted mild nasal congestion and thought that the flushes were less intense, but these did not change in appearance nor in rate of recurrence. The range of daily urine excretion of 5-hydroxyindoleacetic acid was unaltered.

Oral Administration of Chlorpromazine. Chlorpromazine was given to case 2 by mouth in daily doses of 100 mg. for 9 months. The patient meticulously kept a daily record of the number and intensity of flushing attacks for 3 months before and during the taking of the drug. The number of flushes did not decrease, and actually became more frequent; however, the intensity and duration of flushing attacks significantly lessened. This was accompanied by a decrease in the severity of the diarrhea and in the frequency of episodes of vomiting and abdominal pain. There was no significant change in average daily urinary excretion of 5-hydroxyindoleacetic acid.

Effects of Intravenously Administered Bromo-LSD

Psychic Effects. In man small doses of bromo-LSD are said to produce none of the bizarre psychic effects noted with lysergic acid diethylamide[23, 31] but this is not the case when bromo-LSD is administered intravenously in large doses. Thus, when constant intravenous infusions of bromo-LSD were given to 2 normal subjects (cases 5 and 6) both experienced psychic changes, which became more severe as the infusion continued and persisted for 3 to 4 hours after the infusion was stopped. No hallucinations were noted but there were feelings initially of drowsiness, depression, anxiety and apprehension, followed by feelings of irritation, restlessness, and tenseness, and later, intensely disagreeable sensations of unreality and depersonalization, inexplicable feelings of strangeness and mild confusion. On a subsequent day, both these subjects and another normal subject (case 7) received constant intravenous infusions of serotonin, followed in 10 to 44 minutes by a simultaneous infusion of bromo-LSD. Psychic changes were also experienced during the simultaneous infusions of serotonin and bromo-LSD, although the mental disturbances seemed somewhat less intense than when bromo-LSD was given alone. Furthermore, all other subjects (cases 1–4) have noted similar psychic changes during and after infusion of bromo-LSD; these changes were not modified by single injections of 2 to 4 mg. of serotonin.

Effect on Cardiac Functions. The data obtained during cardiac catheterization in case 1 are summarized in table 1. Pressure tracings indicated no significant valvular lesions. The

difference in oxygen concentration in the pulmonary artery and the right ventricle was not indicative of left-to-right shunt. There was no elevation of pulmonary artery pressure. The resting control systemic resistance of 727 dynes was low compared to a normal mean of about 1250 dynes.

An intravenous infusion of bromo-LSD (1 mg. per minute) was started and determinations were repeated after 10 minutes of infusion. Bromo-LSD had no effect on pulmonary artery pressures. The systemic mean pressure was unchanged. Cardiac output fell slightly from 8.8 to 7.9 L. per minute. The systemic and the total pulmonary resistance changed little during the infusion.

There was no significant difference between serum serotonin levels in hepatic venous blood, mixed venous blood, and peripheral arterial blood, and no appreciable changes in these concentrations during the infusion of bromo-LSD.

Influence on Vascular Action of Norepinephrine (*table 2*). Injections of norepinephrine prior to infusion of bromo-LSD were followed in all subjects, both carcinoid (cases 1 and 2) and normal (cases 3, 4, and 5), by swift rises of arterial pressure of from 20 to 56 mm. Hg systolic and 3 to 32 mm. Hg diastolic. In both carcinoid patients norepinephrine provoked flushing of the face and neck, which appeared as the pressure fell to or below the control level. Arterial pressure did not change appreciably during the intravenous infusion of bromo-LSD nor did the pressor responses to norepinephrine; flushing of the skin occurred in case 1 but not in case 2.

Influence on Vascular Action of Serotonin (*table 3*). Prior to the infusion of bromo-LSD, single intravenous injections of serotonin in both control and carcinoid subjects were followed by flushes of the skin similar to spontaneous attacks occurring in the carcinoid patient and by pressor responses of 29 to 58 mm. Hg systolic and 9 to 57 mm. Hg diastolic (table 3). The flush, involving the face, neck, and extremities, was intense in 4 patients and mild in 1 (case 5). Subjective discomfort was profound in all subjects and characterized by nausea,

TABLE 1.—*Cardiac Catheterization Data in Case 1 before and during Intravenous Infusion of 2-Bromo-d-Lysergic Acid Diethylamide* (*Bromo-LSD*)

	At rest	During bromo-LSD
O_2 consumption (ml./min.)	266.5	278.8
O_2 capacity (vol. per cent)	17.4	—
O_2 content systemic artery (vol. per cent)	16.0	16.0
O_2 content pulmonary artery (vol. per cent)	13.0	12.5
A-V O_2 difference (vol. per cent)	3.0	3.5
Cardiac output (L./min.)	8.9	7.9
Mean pulmonary artery pressure (mm. Hg)	15.0	15.0
Systemic resistance (dynes-sec.-cm.$^{-5}$)	727	770
Total pulmonary resistance (dynes-sec.-cm.$^{-5}$)	144	150
Mean brachial artery pressure (mm. Hg)	80	77
Serum serotonin (μg./ml.)		
Hepatic vein	1.1	—
Brachial artery	1.0, 0.7	1.1
Pulmonary artery	1.4	1.1

TABLE 2.—*Arterial Pressure Responses to Single Intravenous Injections of Norepinephrine before and during Intravenous Infusion of 2-Bromo-Lysergic Acid Diethylamide* (*Bromo-LSD*)

Case	Control B. P., mm. Hg	Before bromo-LSD		During bromo-LSD		
		Norepinephrine, 10 μg. i.v.		Bromo-LSD, mg./min.	Norepinephrine, 10 μg. i.v.	
		B.P. response, mm. Hg	Flush		B.P. response, mm. Hg	Flush
1. Carcinoid	98/63	+30/32	+	1.0	+29/27	+
2. Carcinoid	152/95	+56/23	+	0.5	+31/26	0
3. Control	140/98	+22/17	0	1.0	+25/32	0
4. Control	128/73	+42/17	0	5.0	+30/25	0
5. Control	125/72	+20/3	0	1.0	+20/16	0

+ = mild.

TABLE 3.—*Arterial Pressure Responses to Single Intravenous Injections of Serotonin before and during Intravenous Infusion of 2-Bromo-d-Lysergic Acid Diethylamide (Bromo-LSD)*

Case	Control B.P., mm. Hg	Before bromo-LSD		During bromo-LSD		
		Serotonin, 2–4 mg. i.v.		Bromo-LSD, mg./min.	Serotonin, 2–4 mg. i.v.	
		B.P. response, mm. Hg	Flush		B.P. Response, mm. Hg	Flush
1. Carcinoid	95/60	+48/41	+++	1.0	+47/44	++
2. Carcinoid	151/96	+54/35	++	0.5	+55/55	0
3. Control	143/96	+58/57	+++	1.0	+27/29	0
4. Control	128/75	+47/18	+++	5.0	+20/20	+
5. Control	122/82	+29/9	+	1.0	+33/3	++

\+ = mild.
++ = moderate.
+++ = marked.

paresthesias, breathlessness, and an urge to empty the bowel and bladder. These effects were transient and lasted for about the same length of time, 2 to 3 minutes, as the rise in arterial pressure.

Single injections of serotonin during the infusion of bromo-LSD failed to provoke flushing in cases 2 and 3, the flush was less intense and diffuse in cases 1 and 4, but actually seemed more marked in 1 control subject (case 5). The pressor response in all subjects was similar to that observed when serotonin had been injected alone. The other effects of serotonin were usually milder and less uncomfortable for most subjects, but 1 control subject (case 5) found that the subjective discomfort due to serotonin was intensified during the infusion of bromo-LSD.

DISCUSSION

Demonstration of large quantities of serotonin in carcinoid tumor extracts,[9] hyperserotonemia,[13, 14] and increased urinary excretion of serotonin end-products[15] in carcinoid patients, all implicate serotonin in the pathogenesis of the vasomotor episodes. This assumption is supported by precipitation of flushes in some patients by palpation of the tumor.[13, 32, 33] Flushing was said not to occur as a result of intravenous injections of serotonin in man;[34-36] intravenous infusions of 0.8 to 1.2 mg. per minute of serotonin creatinine sulfate produced tingling and burning of the face but no flush was seen.[15] However, in the present study, rapid single intravenous injections of larger (1.8 to 4.0 mg.) doses of serotonin provoked mild to moderate, at times intense, flushes in normal as well as carcinoid subjects. This was also observed in hypertensive patients.[37] The flushes appeared to be similar in every way to the paroxysmal attacks in carcinoid patients.

Hypotension and syncope accompanied by flushing was observed in several carcinoid patients.[13, 33, 38] One of our carcinoid patients (case 1) had, at rest, a low systemic resistance, and lowering of his arterial pressure by several different agents was invariably followed by attacks of flushing. This suggests that hypotension either directly or by vasomotor reflexes stimulates the tumor to release increased amounts of serotonin into the blood. Either assumption presupposes that the tumor is innervated.

The intermittent character of flushing attacks in the carcinoid syndrome is most likely associated with variations in the output of serotonin by the tumor; another possibility might be episodic changes in the proportion of free, biologically active serotonin to platelet-bound serotonin circulating in the peripheral blood. It is unlikely that a generalized parasympathetic discharge is involved, since flushing was not prevented by atropine or tetraethylammonium chloride.

An oral dose of BAS of 400 mg. a day failed to relieve symptoms or produce sedation in case 1. This lack of sedative effect contrasts with that reported[39] in hypertensive patients given much smaller amounts (160 mg. per day). Bromo-LSD administered by mouth in doses up to 20

mg. daily also failed to relieve flush and diarrhea in case 2; smaller oral doses of bromo-LSD (1 to 15 mg. a day) did not antagonize the circulatory effects of serotonin in other carcinoid subjects.[38, 40, 41] The dosages of these antimetabolites may be inadequate but they were larger than those used before and increased doses did not seem practicable.

Intravenous infusion of bromo-LSD in large doses (0.5 to 5.0 mg. per minute) did not effectively block the pressor response to serotonin. Serotonin-induced flush and other pharmacologic effects of serotonin were diminished or failed to appear in some subjects during infusion of bromo-LSD but this was not a consistent observation; in 1 normal subject (case 5) there was an aggravation of all reactions to serotonin. In normal rats, bromo-LSD (2.5 Gm. per Kg. intravenously) inhibited the effects of subsequent injections of serotonin on arterial pressure and renal function,[25] but had little effect when given during serotonin infusion, an observation consistent with the failure of this agent to influence the course of the carcinoid syndrome.

Chlorpromazine was reported to alleviate the diarrhea of a patient with malignant carcinoid.[42] In our experience, administration of chlorpromazine to a carcinoid patient (case 2) decreased the intensity of flushing attacks and the severity of abdominal symptoms, but had no effect on 5-hydroxyindoleacetic acid excretion.

Lysergic acid diethylamide, a potent serotonin antagonist[43] induces in man temporary mental aberrations accompanied by hallucinations.[44] It was postulated by Woolley and Shaw[45] that these psychic effects might arise by inhibition of the action of serotonin in the central nervous system. This hypothesis was questioned by Cerletti and Rothlin,[23] since 2-bromo-d-lysergic acid diethylamide in doses of 1 to 2 mg. (20 times as great as lysergic acid) did not produce psychic disturbances in man even though it was a potent serotonin antagonist in vitro. We have found that large doses (a total of 15 to 160 mg.) of bromo-LSD, given by constant intravenous infusion, provoked definite psychological changes in all normal subjects who received the drug, as well as in 2 carcinoid patients. The intensity of the subjective response to the drug appeared to be dependent, in part, on the cultural background and ability for self-observation of the subject, and, in part, to the total amount of drug received. The mental changes did not include hallucinations but were similar in most other respects to those induced by LSD.

The relatively weak central nervous effects of bromo-LSD, as compared to LSD, could be due to more rapid metabolism and excretion from the body, to lesser ability to penetrate brain tissue or to less powerful binding by receptor sites. Serotonin does not appear to penetrate the blood-brain barrier to any appreciable extent. Thus, although the psychic effects of bromo-LSD, like those of LSD,[46] might be due to serotonin antagonism, it was to be expected that such mental disturbances were not prevented by the hyperserotonemia present in carcinoid patients, nor effectively antagonized by intravenous infusions of serotonin in normal subjects.

Conclusions

Intravenously administered serotonin in man in sufficient dosage caused flushing and reproduced other clinical manifestations of the carcinoid syndrome. Lowering of the arterial pressure in 1 carcinoid patient invariably provoked attacks of flushing, suggesting that hypotension directly or through vasomotor reflexes may stimulate the tumor to liberate excessive amounts of serotonin.

1-Benzyl-2,5 dimethyl serotonin (BAS) and 2-bromo-d-lysergic acid diethylamide (bromo-LSD), though potent serotonin antagonists in vitro, were ineffective in controlling symptoms in carcinoid patients when given by mouth. Chlorpromazine appeared to be partially effective in alleviating the symptoms of the carcinoid syndrome and may be of value in the symptomatic relief of the carcinoid syndrome.

Bromo-LSD, when intravenously administered, did not effectively block, although it may have diminished, the vascular and other pharmacologic effects of intravenously injected serotonin. Bromo-LSD did not cause hallucinations, but in large intravenous doses produced psychic disturbances that otherwise

resemble those regularly observed after small doses of lysergic acid diethylamide. These psychic effects of bromo-LSD might be due to inhibition of some central nervous action of serotonin but they were not prevented by the hyperserotonemia present in carcinoid patients and were not alleviated by infusions of serotonin in normal subjects, as was to be expected by the failure of serotonin to pass the blood-brain barrier.

Acknowledgment

We are indebted to Dr. R. Bircher of Sandoz Pharmaceuticals, Hanover, N. J., for the supply of bromo-LSD (BOL 148); and to Dr. D. W. Woolley, The Rockefeller Institute for Medical Research, New York, for the supply of BAS.

Summario in Interlingua

Le administration intravenose de serotonina in homines—in doses sufficiente—causava enchymose e reproduceva altere manifestationes clinic del syndrome carcinoide. In un caso, le reduction del pression arterial in le presentia del syndrome carcinoide resultava invariabilemente in attaccos de enchymose. Isto pare indicar que hypotension es capace—directemente o via reflexos vasomotori—a stimular le tumor a liberar excessive quantitates de serotonina.

1-Benzyl-2,5-dimethyl-serotonina (BAS) e 2-bromo-d-(acido lysergic)-diethylamido (bromo-LSD)—ben que ambes es potente antagonistas a serotonina in vitro—nonsuccedeva, post administrationes oral, a subjugar le symptomas in patientes carcinoide. Chlorpromazina pareva esser partialmente efficace in alleviar le symptomas del syndrome carcinoide e va possibilemente esser de valor in le alleviamento symptomatic del syndrome carcinoide.

Bromo-LSD in administration intravenose non blocava efficacemente (ben que illo possibilemente reduceva) le effectos vascular e alteremente pharmacologic de serotonina in injectiones intravenose. Bromo-LSD non causava hallucinationes, sed post le administration de grande doses intravenose illo produceva distributiones psychic que resimilava le effectos regularmente observata post parve doses de diethylamido de acido lysergic. Il es possibile que este effectos psychic de bromo-LSD resulta del inhibition del un o del altere action de serotonina in le systema nervose central, sed illos non esseva prevenite per le hyperserotonemia que es presente in patientes carcinoide, e illos non esseva alleviate per infusiones de serotonina in subjectos normal, como on haberea expectate lo, viste le facto que serotonina non transpassa le barriera sanguino-cerebral.

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Medical Eponyms

By Robert W. Buck, M.D.

D'Espine's Sign. In an article entitled "The Sea Cure of Scrofula at the Dollfus Asylum of Cannes" (*La cure marine de la scrofule à l'asile Dollfus de Cannes*) in the *Bulletin de l'académie* 52: 400–420 (November 8) 1904, Adolphe D'Espine (1846–1930) says:

"The first signs of bronchial adenopathy are obtained by auscultating the voice and are nearly always found in the immediate neighborhood of the vertebral column between the seventh cervical vertebra and the first dorsal vertebra, either in the sub-spinous fossa or lower in the interscapular space. These signs consist in a super-added timbre in the voice which one may call a whisper in the first stage and bronchophony in a more advanced stage."

A more complete description of the sign occurs in the article "Early Diagnosis of Tuberculous Bronchial Glands in Children" (*Le diagnostic précoce de la tuberculose des ganglions bronchiques chez les enfants*) in the *Bulletin de l'Académie de Médecine* 57: 167 (January 29) 1907, as follows:

"We have the patient pronounce as clearly as possible *trois cent trente-trois*. In the case of infants, we must be content with auscultation while the child is crying. We first listen over the cervical vertebrae with a small-mouthed stethoscope. . . . We then distinctly perceive, as Laennec pointed out, the characteristic tracheal murmur. . . . In the normal infant this tone stops suddenly at the level of the spinous process of the seventh cervical vertebra where the lung begins.

"In bronchial adenopathy, on the other hand, the bronchial tone is heard over a variable area extending between the seventh cervical and the fourth and fifth dorsal vertebrae. . . .

"When auscultation of the spoken voice or of the cry fails to give any result, we ask the child, if he is old enough to understand, to speak in a whisper, when, if there is adenopathy, an acoustic phenomenon is heard analogous to Bacelli's aphonic pectoriloquy. . . ."

Successful Surgical Repair of a Ruptured Aneurysm of the Sinus of Valsalva

By Andrew G. Morrow, M.D., F.A.C.S., R. Robinson Baker, M.D., Hans Erik Hanson, M.D., and Thomas W. Mattingly, M.D.

A patient is described in whom an aneurysm of the right coronary sinus of Valsalva ruptured into the right atrium. A new method of surgical closure is presented along with pertinent physiologic data obtained before and after operation.

AN EXPERIMENTAL method for the surgical repair of ruptured sinus of Valsalva aneurysm has previously been described.[1] In these experiments, acute cardio-aortic fistulas were produced in dogs and subsequently closed by means of a plastic prosthesis introduced through the aorta during a brief period of occlusion of inflow. We have recently had the opportunity to perform this operation in a patient in whom an aneurysm of the right coronary sinus had ruptured into the right atrium.

Case Report

N. H., a 27-year-old soldier, was first admitted to the National Heart Institute in March 1956. His past health had been excellent and several physical examinations prior to his illness had revealed no evidence of heart disease. While sitting at his desk on January 9, 1956, the patient noted the sudden onset of chest pain, shortness of breath, and epigastric discomfort. These symptoms persisted and he was admitted to an Army Hospital, where his acute symptoms subsided following administration of digitalis and sodium restriction. The patient was subsequently referred to the Walter Reed Army Hospital. Physical examination at that time revealed bounding peripheral pulses and a blood pressure of 130/0 mm. Hg. Systolic and diastolic thrills were palpable along the left sternal border. A loud continuous murmur was heard over the precordium. There were also right pleural effusion, hepatomegaly, and pretibial edema. A right heart catheterization revealed a left-to-right shunt at the level of the right atrium. With these findings a diagnosis of ruptured aneurysm of the sinus of Valsalva was made and the patient was transferred to the National Heart Institute for study.

From the Clinic of Surgery, National Heart Institute, Bethesda, Md. and the Cardiology Service, Walter Reed Army Medical Center, Washington, D. C.

On March 6, 1956, a no. 9 Lehman catheter was passed from the right ulnar artery into the ascending aorta and its tip was positioned just above the aortic valve. Simultaneous pressures were recorded from this catheter and a Cournand needle in the femoral artery (fig. 1). The pressure pulses were similar to those seen in moderately severe aortic insufficiency. The catheter was then passed from the aorta into the right atrium, establishing the presence of an aortic-right atrial communication. Following this, the catheter was again positioned above the valve and 60 ml. of 70 per cent acetrizoate (Urokon) were injected as biplane x-rays were made at the rate of 4 per second. These films demonstrated dilatation of the right coronary sinus of Valsalva from the base of which dye passed into the right atrium (fig. 2).

Following aortography the patient returned to Walter Reed Army Hospital, where he was maintained on digitalis, sodium restriction, and mercurial diuretics. In spite of these measures, evidence of right heart failure persisted.

He returned to the National Heart Institute on July 4, 1956. At that time he was emaciated and orthopneic, with bounding pulses and a blood pressure of 120/50–0. There were moist rales at the left base and dullness at the right base. The apical impulse was diffuse, and cardiac dullness extended to the left anterior axillary line. There was a regular rhythm. Systolic and diastolic thrills were palpable along the left sternal border. A loud continuous murmur was heard over the entire precordium, with maximum intensity in the fourth left intercostal space. The liver was enlarged and tender, and there was demonstrable ascites. Moderate pretibial edema was present. Upon admission to the hospital, the patient was given 0.5 mg. of digoxin daily and his diet was restricted to 200 mg. of sodium. He lost 8 Kg. during the ensuing 4 weeks. This was accomplished by means of a thoracentesis, paracentesis, and a course of acetazoleamide (Diamox) followed by ammonium chloride and mercuhydrin.

The hematocrit value was 46 mm. and the white cell count was 8,000. The blood urea nitrogen was 17 mg. per cent and the total protein was 6.7 mg.

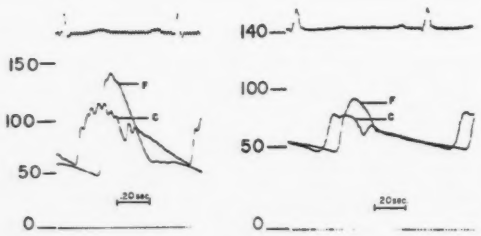

FIG. 1. Preoperative and postoperative central aortic and femoral artery pulse tracings. The femoral/central pulse pressure ratio was 1.7 preoperatively and 1.0 postoperatively.

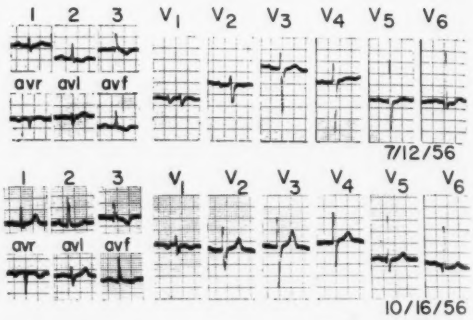

FIG. 3. Preoperative and postoperative electrocardiograms.

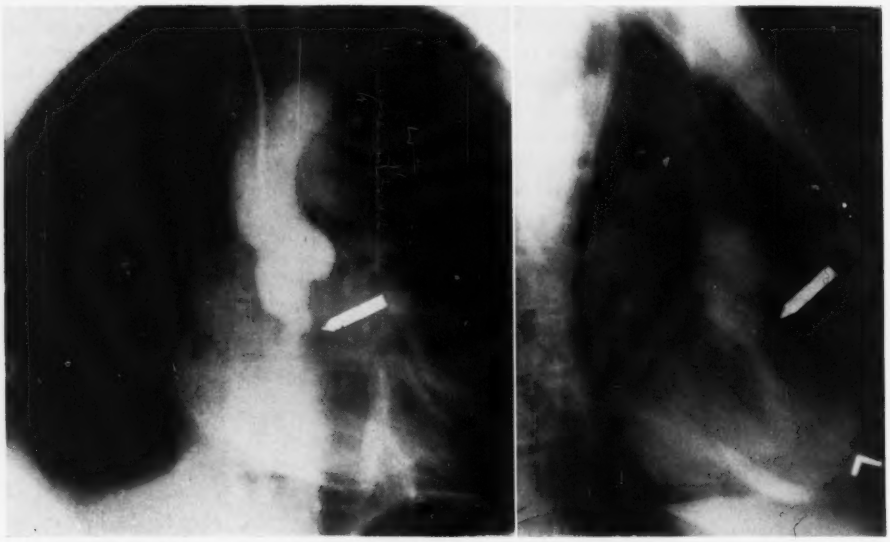

FIG. 2. Thoracic aortogram 1 second after the injection of 60 ml. of 70 per cent Urokon. The right coronary sinus is deformed and a jet of dye is seen entering the right atrium near the tricuspid valve.

per cent, with an albumin of 2.9 mg. and a globulin of 3.8 mg. per cent. Urinalysis was normal. The electrocardiogram showed a normal sinus rhythm and a vertical electric position with a prolonged P-R interval (fig. 3). Films and fluoroscopic examination of the chest showed marked cardiac enlargement both to the right and left with active aortic pulsations. There were bilateral pulmonary congestion and pleural effusion extending to the level of the fourth right interspace anteriorly (fig. 4). The phonocardiogram revealed a clear first sound that was followed by a crescendo systolic murmur enveloping the second heart sound. The second sound was followed immediately by a diastolic murmur that gradually decreased in intensity throughout diastole (fig. 5). Cardiac catheterization revealed moderate pulmonary hypertension and marked elevation of the right atrial pressure. A nitrous oxide test performed in the right atrium revealed a Calloway index of 0.6, indicating the presence of a large left-to-right shunt at this level. This shunt was calculated to be 7.7 L. per minute (table 1).

Operation was performed on August 1, 1956. Following induction of Pentothal and nitrous oxide anesthesia, the patient was immersed in a bath of ice and water until the esophageal temperature fell to 33 C. With the patient in a supine position, a median sternotomy was made and combined with an incision through the right fourth intercostal space (fig. 6). The pericardium was opened anterior to the phrenic nerve. On opening the pericardium, the right atrium was found to be markedly enlarged

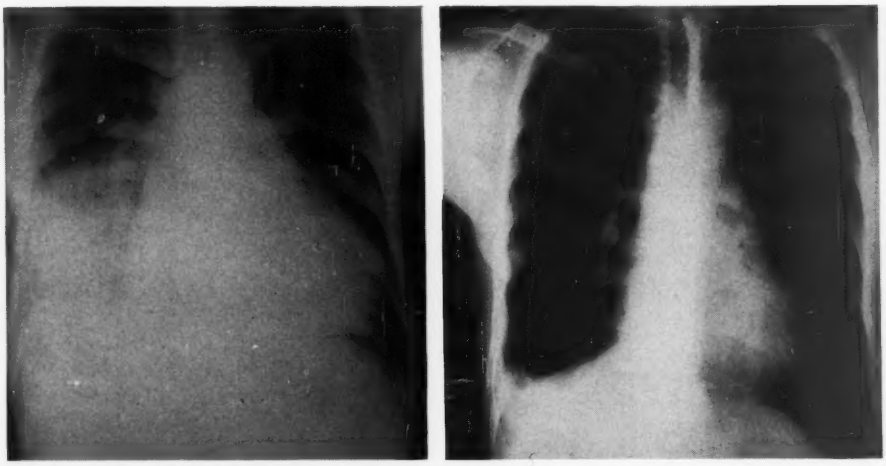

FIG. 4. Preoperative roentgenogram (left) illustrating marked cardiac enlargement, bilateral pulmonary congestion, and a pleural effusion on the right. Postoperative roentgenogram (right) showing the dramatic regression in the size of the cardiac silhouette.

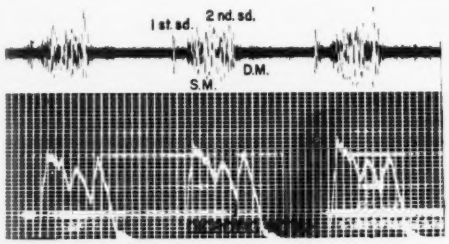

FIG. 5. Preoperative phonocardiogram.

and a continuous thrill was easily palpable over its surface. Upon reflection of the right atrial appendage, the right coronary sinus was found to be enlarged and the wall of the aorta appeared to be thinner than normal. Temporary traction ligatures were then placed around the superior and inferior venae cavae. Digital exploration of the right atrium revealed a grossly enlarged chamber and a normal tricuspid valve. A thin-walled balloon-like structure, approximately 3 cm. in diameter, projected into the atrium just above the septal leaflet of the tricuspid valve. A continuous jet of blood was palpable from a 4 to 5 mm. opening in the tip of this aneurysm. Digital occlusion of this opening resulted in a pronounced rise in the patient's diastolic blood pressure and a marked slowing of the heart rate. The adventitia of the ascending aorta was then excised and a mattress suture was placed in the anterolateral wall of the aorta approximately 3.5 cm. above the aortic valve. A malleable probe was introduced into the aorta through a stab wound within this mattress suture and with the finger again in the

TABLE 1.—*Preoperative Right Heart Catherization*

Samples location	Pressures mm. Hg. Syst./diast.	Pressures mm. Hg. Mean	O_2 content vol. %	Body surface area—1.65 M^2
SVC			8.1	Nitrous oxide test
RA—low	27/15	23	13.4	
RA—mid			12.8	
RA—high			13.4	
RV—inflow	63/29		13.7	
RV—mid			14.0	
RV—outflow			14.0	
PA I	62/28	42	13.9	
FA I			16.2	
PA II			13.8	
FA II			16.0	
Capacity FA			16.9	

Location	Blank	Sample	O_2
SVC	1.20	1.53	8.1
RA	1.51	2.92	12.7
FA	1.58	3.72	15.7

Nitrous index:

$$\frac{\text{RA—SVC}}{\text{FA—SVC}} = 0.60$$

Pulmonary flow—10.7 L./min.*
Systemic flow—3.0 L./min.*
L-R shunt—7.7 L./min.

	Ventilation L./min./M^2	O_2 Consumption ml./min./M^2	R.Q.	Pul. flow L./min./M^2	% Sat.
Rest I	4.62	130	.78	6.54	96.6
Rest II	4.62	162	.85	7.4	

* Average of 2 determinations.

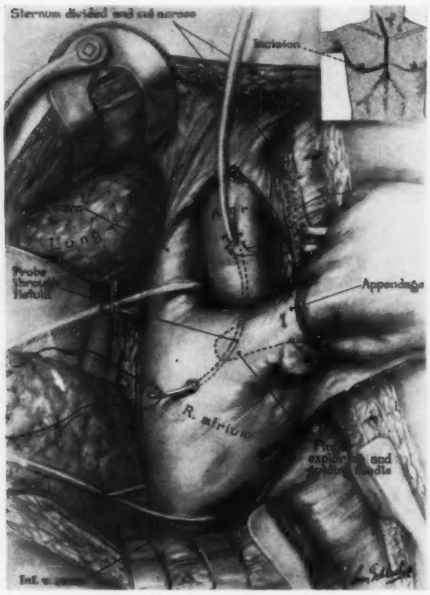

FIG. 6. A malleable probe was introduced through a stab wound in the aorta and advanced through the fistula and subsequently through the right atrial wall. A ligature was then drawn through the fistula and out of the aorta.

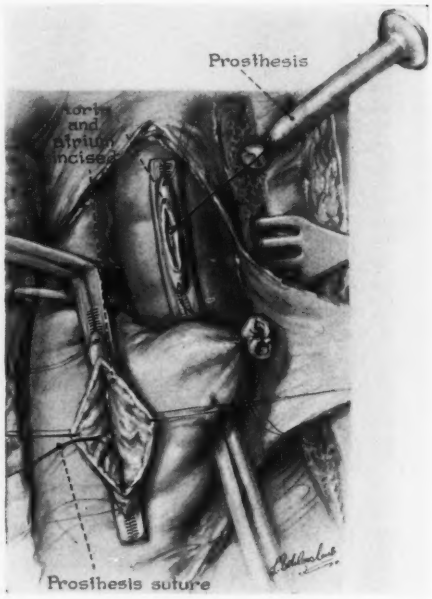

FIG. 7. Incisions were made in the aorta and right atrium after the application of clamps, and the prosthesis was tied to the aortic end of the ligature.

right atrium as a guide, it was passed through the fistulous tract and out into the right atrium. The tip of the probe was subsequently advanced through the right atrial wall and a ligature of heavy silk threaded into the eye of the probe (fig. 6). The probe was then withdrawn from the aortic incision and the mattress suture tied down to control hemorrhage from the small aortic incision. The ligature thus passed into the aorta, through the fistulous tract and out through the wall of the right atrium. A number of compressed polyvinyl prostheses had previously been prepared[1] and sterilized by boiling. One of these with a head of 2.5 cm. and a shaft of 9 mm. in diameter was selected. The tail of this prosthesis was sutured to the end of the ligature emerging from the aorta (fig. 7). Incisions were then made in the aorta and right atrium following the application of partially occluding clamps.

The superior and inferior venae cavae were occluded and after a period of 1 minute, the clamps were removed from the aortic and right atrial incisions. Traction was made on the atrial end of the ligature and the prosthesis was drawn into the ascending aorta. The head of the prosthesis was guided into place behind the right coronary leaflet by means of a finger introduced through the aortic incision (figs. 8 and 9). The partially occluding clamp was then reapplied to the aortic incision and

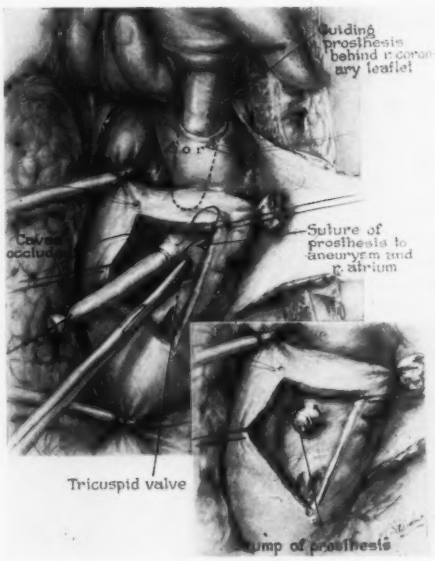

FIG. 8. After occlusion of inflow the prosthesis was pulled into the aorta and positioned behind the right coronary leaflet. A purse-string suture was placed around the base of the prosthesis securing it to the right atrial wall.

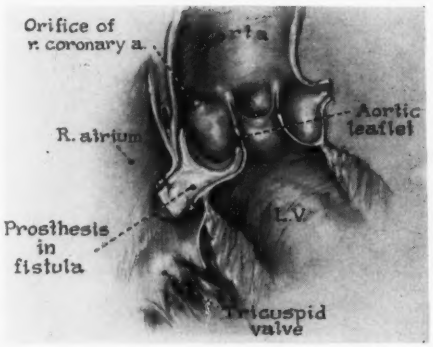

FIG. 9. Cross section at the level of the aortic valve, showing the final position of the prosthesis.

TABLE 2.—*Postoperative Right Heart Catheterization*

Samples location	Pressures mm. Hg. Syst./Diast.	Mean	O_2 content vol. %
SVC		3	12.7
			11.4
IVC		5	13.3
			12.5
RA—low		3	13.0
RA—mid			12.5
RA—high			12.4
RV—inflow	22/4		12.9
RV—mid			11.6
RV—outflow			10.9
PA I	21/10	15	12.2
FA I	110/60	70	16.4
PA II			12.0
FA II			16.2
Capacity FA			17.6

Body surface area—1.68 M.²

Nitrous oxide test

Location	Blank	Sample	O_2
Fem. Vein	1.43	1.42	14.7
RA	1.40	1.70	11.5
FA	1.37	4.84	16.6

Nitrous index:

$$\frac{RA - SVC}{FA - SVC} = 0.08$$

Pulmonary flow—5.7 L./min.
Systematic flow—5.7 L./min.
L-R shunt—0 L./min.

	Ventilation L./min./M.²	O_2 consumption ml./min./M.²	R. Q.	Cardiac index L./min./M.²	% Sat.
Rest I	3.78	147	.73	5.9	94.7
Rest II	3.51	138	.72	5.5	

attention directed to the right atrium. The proximal portion of the prosthesis tightly occluded the fistulous tract while the remainder of the shaft projected into the atrial chamber. The thin wall of the aneurysm everted itself upon the shaft of the prosthesis. A purse-string suture was then placed around the base of the prosthesis securing it to the right atrial wall. The remainder of the shaft was cut off distal to this suture. The atrial clamp was then reapplied and circulation was re-established. The total period of caval occlusion was 4 minutes. During occlusion the patient's esophageal temperature was 27 C. The aortic and atrial incisions were closed with continuous over-and-over sutures. Following decortication of the right lower lobe, drainage tubes were placed in the right pleural space and the chest was closed.

The patient's course after operation was uneventful. The pulse rate ranged between 40 and 50 per minute for 3 days postoperatively and then gradually increased to normal. The murmur was no longer present and the diastolic blood pressure was 70 mm. Hg. He was discharged on August 31, 1956, entirely free of symptoms.

The patient returned for postoperative studies in October 1956. He continued to be asymptomatic and had gained 8 Kg. The electrocardiogram (fig. 3) and roentgenogram (fig. 4) confirmed the clinical improvement. Right heart catheterization revealed normal pressures and no evidence of a left-to-right shunt (table 2). Measurements of central and peripheral arterial pressures were now normal (fig. 1).

DISCUSSION

The sudden onset of heart failure in a previously well individual should suggest the diagnosis of ruptured aneurysm of the sinus of Valsalva. As illustrated in the case presented, the most definitive diagnostic study is thoracic aortography. Right heart catheterization affords an estimate of the magnitude of the shunt and the degree of cardiac disability.

This patient presented an unusual opportunity for the correlation of central and peripheral arterial pressures with a measurable degree of aortic regurgitation. Preoperatively the ratio of femoral-to-central aortic pulse pressure was 1.73—a value seen in moderately severe aortic insufficiency. From the calculation of systemic and pulmonary flows this abnormally high femoral-to-central ratio represents the regurgitation of 7.7 L. per minute with an effective forward systemic flow of only 3.0 L. per minute. It is realized, of course, that in this instance regurgitant flow occurred throughout the cardiac cycle as contrasted to true aortic insufficiency where regurgitation occurs only in diastole. The ratio of femoral-to-central pulse pressure was 1.0 postoperatively, a value within the normal range.

By the application of hydraulic formulas,* [2] the diameter of the fistula was calculated to be 6.8 mm. Although at operation it was difficult accurately to assess the diameter of the opening in the aneurysm, the derived figure was considered to be a close approximation. This assessment was further confirmed by the fact that the shaft of the prosthesis was 9 mm. in diameter and wedged itself tightly into the tract.

Edwards and Burchell[3] have recently emphasized that the essential pathologic lesion of aneurysms of a sinus of Valsalva is a lack of continuity between the aortic media and the aortic ring. The method of closure described above would seem to satisfy the criteria suggested by these authors: ". . . it is obvious that for repair of the aneurysm the defect between the aortic media and the aortic valve ring must be bridged either directly or, more reasonably, indirectly by a prosthetic body." Lillehei[4] and Bahnson[5] have recently successfully closed cardio-aortic fistulas by sutures placed via the right heart during total cardiac by-pass. The technic employed in this patient would seem preferable, since the aortic defect is closed without tension and the aneurysm and fistulous tract are obliterated.

In retrospect, certain modifications in the operative technic would seem desirable. The combined median sternotomy and right thoracotomy did not provide ideal exposure of the ascending aorta. A bilateral anterior thoracotomy would be preferable. When the venae cavae were occluded, the heart did not empty well, since large volumes of blood were constantly returned to the right heart through the fistula. The fistula should have been closed digitally before the cavae were occluded. This would have prevented unnecessary blood loss when the atrium was opened. Although hypothermia afforded adequate time for the insertion and fixation of the prosthesis, the procedure could probably be performed more deliberately with extracorporeal circulation aided by either elective cardiac arrest or retroperfusion of the coronary sinus.

* Regurgitant area = $\frac{\text{Mean regurgitant flow}}{44.5\sqrt{FA_M - RA_M}}$

Calculated shunt = 7.5 L./min.
Mean FA = 85 mm. Hg
Mean RA = 23 mm. Hg

Regurgitant area = $\frac{7500}{60}/44.5\ 85\text{-}23$

Regurgitant area = 0.36 cm.^{2}
Diameter of regurgitant area = 6.8 mm.

Summary

A patient is described in whom an aneurysm of the right coronary sinus of Valsalva had ruptured into the right atrium. The diagnosis was established by thoracic aortography and right heart catheterization. The cardio-aortic fistula was successfully closed by a plastic sponge prosthesis introduced via the aorta during a brief period of occlusion of inflow. Hemodynamic observations before and after operation are described.

Summario in Interlingua

Es describite un patiente in qui un aneurysmo del sinus dextero-coronari de Valsalva se habeva rupturate a in le atrio dextere. Le diagnose esseva establite per aortographia thoracic e catheterisation dextero-cardiac. Le fistula cardio-aortic esseva claudite a bon successo per medio de un prosthese consistente de un spongia de plastico introducite via le aorta durante un breve periodo de occlusion del influxo. Observationes hemodynamic ante e post le operation es describite.

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Combined Mitral and Pulmonic Stenosis

By Herbert Shubin, M.D., David C. Levinson, M.D., and Maurice H. Rosenfeld, M.D.

A CASE of coexisting stenosis of the mitral and pulmonic valves is described. Cardiac catheterization on a patient with stenosis of these 2 valves has not been reported to our knowledge. Gibson and Wood,[1] however, described 1 case with coexisting stenosis of these 2 valves and the tricuspid valve as well.

A modification of the formula for calculating pulmonic valvular resistance is described.

Case Report and Methods

A 56-year-old Caucasian woman was well until the age of 25, when she had a full-term uncomplicated pregnancy. Several days following delivery, she first developed left precordial chest pain and was told by a physician that she had rheumatic heart disease with mitral stenosis. She had no history of rheumatic fever. The chest pain recurred intermittently for several days. She then became asymptomatic until the age of 32, when during the course of her second pregnancy, she first developed palpitation. The palpitation occurred infrequently at first, then with increasing frequency in the past 10 years, often 2 to 3 times per week with individual episodes lasting from several minutes to several days. On various occasions, they have been recorded by electrocardiogram as showing atrial tachycardia and atrial fibrillation. Quinidine was variably effective in terminating these paroxysmal attacks.

In April 1952, she had an initial episode of pulmonary edema. She was awakened from sleep with palpitation and dyspnea. Moist rales were present throughout both lung fields. She was treated with morphine sulfate and quinidine, and the pulmonary edema subsided as her heart rate slowed. An electrocardiogram taken after this episode showed first degree heart block (P-R interval of 0.22 second).

In April 1953, and again in March 1954, she had episodes of pulmonary edema arousing her from sleep and associated with marked tachycardia. As the cardiac rate returned to normal, the pulmonary edema subsided.

In December 1954, she had her first documented attack of paroxysmal atrial flutter, with the electrocardiogram showing a 2:1 atrial flutter. This arrhythmia was converted to a sinus rhythm with digitalis. Prior to this episode, she had not been treated with digitalis.

In July 1955, she had a paroxysm of atrial flutter that converted to atrial fibrillation while she was being digitalized, and subsequently to sinus rhythm with quinidine therapy. She has remained on digitalis since then, and has taken quinidine intermittently.

Aside from the periods of paroxysmal tachycardia, she has not had dyspnea on moderate exertion or undue fatigue. She has also been free of angina.

Physical examination disclosed a well developed woman in no discomfort. There was no cyanosis of the skin. The neck veins were not distended. The thyroid gland was not enlarged. The chest was symmetrical and moved well bilaterally. The lungs were clear to percussion and auscultation. The left lateral border of cardiac dullness extended to the fifth interspace in the midclavicular line. The point of maximum impulse and the apex beat were in the fifth interspace just medial to the midclavicular line. There was a diastolic thrill at the apex. The mitral first sound was loud. The pulmonic second sound was split and louder than the aortic second sound. An opening snap was heard at the left nipple area. A grade I blowing systolic murmur was heard at the pulmonic area. A grade I pandiastolic rumble was present at the apex (fig. 1). The rhythm was atrial fibrillation with a ventricular rate of about 70. The blood pressure was 100/65 mm. Hg in the right arm and 112/72 mm. Hg in the right leg. Femoral pulsations were strong. The liver and spleen were not felt. The extremities showed no edema, clubbing, or deformity.

The hemoglobin was 11 Gm., white blood count was 10,000, with the 70 per cent polymorphonuclear cells, 27 per cent lymphocytes, and 1 per cent each of eosinophils, basophils, and monocytes. The hematocrit level was 39 per cent. The urine was negative, the blood urea nitrogen was 12 mg. per 100 ml.

The electrocardiogram showed atrial fibrillation. The vectorcardiogram was normal.

Chest x-ray and fluoroscopy showed no enlargement of the heart. There was a double contour produced by moderate enlargement of the left atrium. There was a moderate increase in the angulation of the bifurcation of the trachea to 90° in the posteroanterior projection (normal less than 75°) and to a 65° angle in the left anterior oblique projection (normal less than 35°). There was slight posterior encroachment of the enlarged left atrium on the

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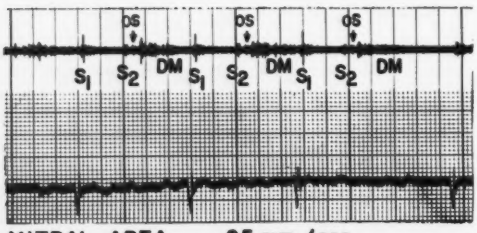
This work was made possible by a grant from The United Hostesses.



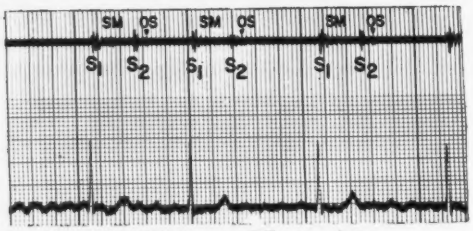


FIG. 1. S_1, first heart sound; S_2, second heart sound; *OS*, opening snap; *DM*, diastolic murmur; *SM*, systolic murmur.

esophagus. The vascular markings in the lungs were normal (fig. 2).

Cardiac catheterization was performed in March 1956 (table 1). An abrupt pressure gradient of 13/8 to 38/8 mm. Hg was recorded as the catheter was withdrawn from the main pulmonary artery to the right ventricle (fig. 3), indicating a pulmonic valvular stenosis. The cardiac output of 1.6 L. per minute was unusually low. There was significant venous oxygen desaturation and the A-V oxygen difference was great.

Calculations

Pulmonic Valvular Resistance. The method of determining pulmonic valvular resistance has been altered somewhat from that employed by Dow and co-workers[2] who used the formula

$$PVR = \frac{(RVsm - PAsm) \times 1332}{CO(\text{ml./sec.})} \text{ dynes seconds cm.}^{-5}$$

PVR = Pulmonic valvular resistance. *RVsm* = Right ventricular mean systolic ejection pressure in millimeters of mercury. *PAsm* = Pulmonary artery mean systolic pressure in millimeters of mercury. *CO* = Cardiac output in milliliters per second = pulmonary blood flow in milliliters per second.

As Dow employed the formula, the flow past the pulmonic valve was computed as though it occurred throughout the cardiac cycle. Since the flow past the pulmonic valve occurs only during the systolic ejection phase of each cardiac cycle, the rate of flow per second is obtained by multiplying

$$\text{cardiac output (ml./sec.)} \times \frac{\text{duration of cardiac cycle}}{\text{duration of systolic ejection phase}}$$

Gorlin and Gorlin[3] in calculating pulmonic valve area took note of this point, but did not employ this correction in calculating pulmonic valve resistance.

The formula for calculating pulmonic valve resistance should be

$$PVR = \frac{(RVsm - PAsm) \times 1332}{CO(\text{ml./sec.}) \times \frac{\text{duration of cardiac cycle}}{\text{duration of systolic ejection phase}}}$$

dynes seconds cm.$^{-5}$

The relation of the systolic ejection phase to the cardiac cycle depends on the heart rate. With increases in heart rate, the systolic ejection phase shortens less, proportionately, than the diastolic phase, and therefore occupies a greater portion of each cardiac cycle. The effect of heart rate on the relative duration of the systolic ejection period is corrected in the revised formula.

Stenosis of the valve itself, as has been demonstrated with aortic stenosis, may also prolong the ejection phase of the cardiac cycle. The degree of stenosis may be an additional factor, therefore, in determining the relationship of the systolic ejection period to the total cardiac cycle. The effect of stenosis on the length of the systolic ejection phase is corrected in the revised formula.

In this case, each systolic ejection phase averaged about 0.24 second, and each cardiac cycle about 0.86 second, although with atrial fibrillation, this represents only an average value. The rate of flow past the pulmonic valve was therefore $\frac{0.86}{0.24} = 3.57$ times as great as would be suggested by the cardiac output. The right ventricular mean systolic ejection pressure was 25 mm. Hg and the pulmonary artery mean systolic pressure was 10 mm. Hg. The pulmonic valvular resistance, therefore, was 210 dynes seconds cm.$^{-5}$ Based on this method, normal resistance at the pulmonic valve would be expected to be less than 90 dynes seconds cm.$^{-5}$ This calculation would be based on a cardiac output of 3 L. per minute or greater, a heart rate of about 70, and a difference in mean systolic pressure between the right ventricle and pulmonary artery of 10 mm. Hg or less. With a greater cardiac output per minute, or a smaller difference in mean systolic pressures between the right ventricle and pulmonary artery, the normal resistance at the pulmonic valve would

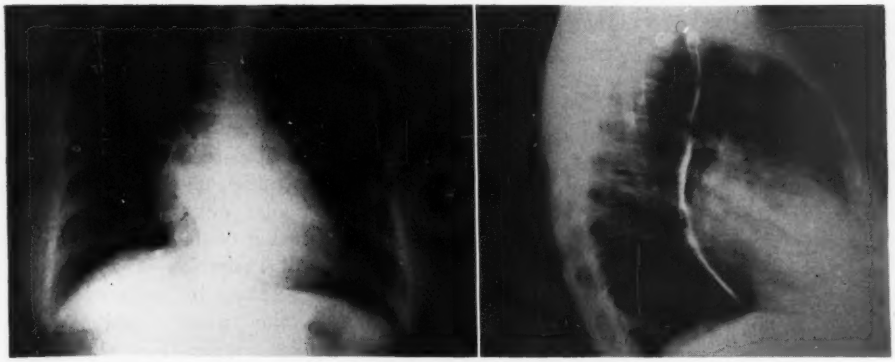


FIG. 2. The arrows on the posteroanterior x-ray of the chest point out the double contour produced by the moderate enlargement of the left atrium. The lateral view of the chest shows slight posterior encroachment of the enlarged left atrium on the esophagus.

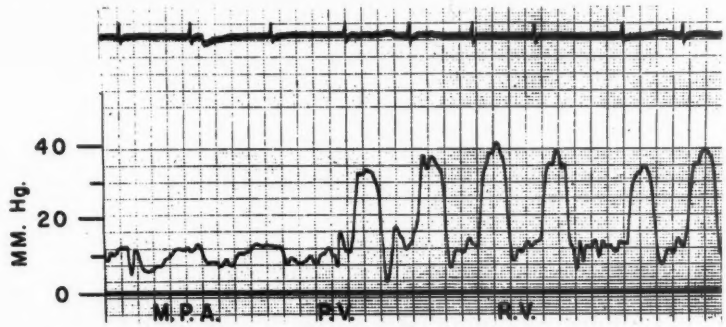


FIG. 3. *MPA*, main pulmonary artery; *PV*, pulmonary valve; *RV*, right ventricle. The pressure changes abruptly between the main pulmonary artery and the right ventricle.

decrease accordingly. Values for pulmonic valvular resistance, by this method, are about one third of those quoted in the literature.[2, 3] This 1:3 ratio may vary appreciably, however, with heart rate or stenosis itself. The revised formula provides a more consistent basis for comparing valve resistance with variations in these 2 factors.

Pulmonic Valve Area. The area of the pulmonic valve may be derived from the formula by Gorlin and Gorlin,[3] where

$$PVA = \frac{PVF}{44.5\sqrt{RVsm - PAsm}}$$

PVA = Pulmonic valve area in cm.^{2} PVF = Pulmonic valve flow in milliliters per second. (i.e., cardiac output in

$$\text{ml./sec.} \times \frac{\text{duration of cardiac cycle}}{\text{duration of systolic ejection phase)}}$$

$RVsm$ = Right ventricular mean systolic ejection pressure in mm. Hg. $PAsm$ = Pulmonary arterial mean systolic pressure in mm. Hg. The pulmonic valve area in this patient is therefore 0.55 cm.^{2}, indicating a considerable degree of stenosis.

Pulmonary Vascular Resistance. The pulmonary vascular resistance proximal to the capillaries may be calculated by the formula

$$PVR = \frac{(PAm - PCm) \times 1332}{CO(\text{ml./sec.})} \text{ dynes seconds cm.}^{-5}$$

PVR = Pulmonary vascular resistance. PAm = Pulmonary artery mean pressure. PCm = Peripheral pulmonary artery (i.e., wedged or capillary) mean pressure. CO = Cardiac output.

The patient had a mean pulmonary artery pressure of 9 mm. Hg and a mean peripheral pulmonary artery pressure of 4 mm. Hg. Her pulmonary vascular resistance was 250 dynes seconds cm.$^{-5}$ Wood[4] has calculated pulmonary vascular resistance in terms of units, where 1 unit represents approximately 80 dynes. By Wood's formula,

$$PVR = \frac{PAm - PCm}{CO(\text{L./min.})}$$

TABLE 1.—*Data Obtained during Cardiac Catheterization*

Station	Pressure (mm. Hg)	O_2 saturation (vols. per cent)	Per cent O_2 saturation
Superior vena cava.	10/8	4.7	31.1
Right atrium.....	10/8	5.3	35.0
Right ventricle.....	38/8	6.3	42.0
Main pulmonary artery.....	13/8	6.3	42.0
Right peripheral pulmonary artery.	5/3		
Femoral artery.....		14.7	97.5

O_2 capacity = 15.1 vols. per cent = 100 per cent saturation. O_2 consumption = 133 ml. per minute. Cardiac output = 1.6 L./min. (Fick principle). Cardiac index = 1.1 L./M.²/min.

By this formula the patient has a pulmonary vascular resistance of 3.1 units. Wood[4] classified pulmonary vascular resistance of 3.9 units or less as normal, and resistance of over 10 units as extreme. He found that pulmonary vascular resistance of more than 10 units would usually protect against the development of pulmonary vascular congestion and dyspnea. Normal pulmonary vascular resistance of 3.9 units or less did not afford this protection. In this case, although the patient had a normal pulmonary vascular resistance of 3.1 units, she did not develop dyspnea on effort, except on those occasions when the dyspnea was brought on by paroxysmal tachycardia. In the presence of a normal vascular resistance, it is considered that the pulmonic stenosis protected her against pulmonary venous congestion and increasing pulmonary capillary pressure.

DISCUSSION

The cardiac output of 1.6 L. per minute is striking. Such a low output might be due to stenosis of either the mitral or pulmonic valves, or both. With so low an output due to mitral stenosis, greatly elevated peripheral pulmonary artery pressure would be expected but the peripheral pulmonary artery pressure was 5/3 mm. Hg. This value would indicate that the pulmonic stenosis exerted a significant limitation on right ventricular output. Both the pulmonic and mitral stenosis must have allowed for some increase in cardiac output under certain circumstances, however, for the moderate exercise that the patient was able to perform would hardly be possible with such a low cardiac output. Despite the low cardiac output she was not in cardiac failure. On 3 isolated occasions associated with paroxysmal tachycardia, she did have transient pulmonary edema. During innumerable other episodes of tachycardia, lasting often up to several days, she did not develop pulmonary edema. During these episodes of tachycardia, the pulmonic stenosis was sufficient, apparently, to prevent right ventricular output from being unduly greater than that of the left.

Mechanical limitation of right ventricular output, other than by pulmonic stenosis, is possible at the tricuspid valve, or by decreased venous return from the body. With marked tricuspid stenosis in the presence of mitral stenosis limitation of cardiac output might also occur at either or both of these valves, depending on the relative stenosis of each. In Gibson's and Wood's[1] series of tricuspid stenoses, both low and normal cardiac outputs were recorded. It is a paradox, however, that in their series, the largest cardiac output (6.8 L. per minute) was recorded in the presence, not only of tricuspid and mitral stenosis, but of a third stenosis, pulmonic as well, indicating that the degree of functional stenosis is the governing factor. Limb tourniquets, like significant tricuspid stenosis, also may limit return to the right ventricle and right ventricular output.

SUMMARY

A case of combined pulmonic and mitral stenosis with cardiac catheterization studies is presented. A modification of the formula for calculating pulmonic valvular resistance is discussed. The importance of calculating cardiac output on the basis of the systolic ejection phase is noted.

The pulmonic valvular resistance by this modified formula was 210 dynes seconds cm.$^{-5}$ The pulmonary vascular resistance was 250 dynes seconds cm.$^{-5}$ The pulmonic valvular resistance tended to protect against the development of pulmonary edema, much as a high pulmonary vascular resistance protects against pulmonary edema.

The right ventricular output, which was 1.6 L. per minute, was limited by the pulmonic stenosis. Other mechanisms that might mechanically limit right ventricular output are signifi-

cant tricuspid stenosis or limb tourniquets. In situations of impending pulmonary edema, any one of these factors that decrease right ventricular output may be advantageous.

Acknowledgment

The authors gratefully acknowledge the assistance of Mrs. Rita Shulman, Mr. Harry Fry, and Miss Beatrice Chasin.

Summario in Interlingua

Es presentate un caso de combinate stenosis pulmonic e mitral, con studios de catheterisation cardiac. Un modification del formula pro le calculation del resistentia del valvula pulmonic es discutite. Es signalate le importantia de calcular le rendimento cardiac super le base del phase de ejection systolic.

Secundo le formula modificate, le resistentia pulmono-valvular esseva 210 dyn/sec/cm^{-5}. Le resistentia pulmono-vascular esseva 250 dyn/sec/cm^{-5}. Le resistentia pulmono-valvular exerceva un effecto protectori contra le disveloppamento de edema pulmonar, in plus o minus le mesme maniera como alte resistentias pulmono-vascular es un protection contra edema pulmonar.

Le rendimento dextero-ventricular amontava a 1,6 l per minuta. Illo esseva limitate per le stenosis pulmonic. Altere mechanismos que es possibilemente capace a limitar le rendimento dextero-ventricular es grados significative de stenosis tricuspide e tourniquets al extremitates. In situationes de imminente edema pulmonar, non importa le qual de iste factores que reduce le rendimento dextero-ventricular es possibilemente avantageose.

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Adams-Stokes Syndrome. Under these circumstances there was produced a group of symptoms and signs having a special character, namely, the combination of slow pulse, pseudo-apoplectic attacks, and murmur propagated into the aorta, while the second sound remained clear. In fact, my observations were based upon, and intended to illustrate, the views of Dr. Adams on fatty degeneration of the heart.—William Stokes. *The Diseases of the Heart and the Aorta.* Dublin, 1854.

Main-Stem Extrasystoles

By HENRY J. L. MARRIOTT, B.M., B.Ch. (OXON.) AND SAMUEL M. BRADLEY, M.D.

Extrasystoles arising in the main stem of the bundle of His are generally regarded as very rare; only 7 examples have been published since their original description by Lewis in 1911 and 2 of these fail to satisfy rigid criteria for diagnosis. Four further examples, encountered in a relatively small series of tracings, are here presented and it is concluded that such extrasystoles are not so much rare as they are overlooked.

EXTRASYSTOLES arising in the main stem of the bundle of His are reported to be very rare.[1, 2] Although first described in 1911 by Lewis,[3] Fletcher[1] was recently able to collect only 6 examples from previous publications[2-7] and he added a seventh of his own. Our experience during the last several months has led us to the conclusion that premature beats fulfilling the criteria of main-stem extrasystoles are not so much rare as they are overlooked. In ignorance of the criteria, and if critical thought is not exercised, it is all too easy to dismiss such extrasystoles as "supraventricular" or "nodal" beats, or to overlook them altogether.

We became aware of the criteria for their diagnosis only when we read Fletcher's recent article. During an arbitrary period of 5 months since then, in the course of interpreting only 1,350 consecutive electrocardiograms in a general hospital, we have noted their occurrence in 4 patients. The number of patients exhibiting the various other types of extrasystoles in this same series of tracings is presented for comparison in table 1.

CASE REPORTS

Case 1. A 40-year-old white woman was admitted for excision of a cyst of the left labium minus. In the past history an attack of rheumatic fever at age 7 was recorded and there had been recurrent attacks of joint pain but no cardiac symptoms had developed. On examination there was no evidence of cardiac enlargement but there was a grade 2 blowing systolic murmur heard at the apex; blood pressure was 135/68. An electrocardiogram was normal; one main-stem extrasystole was noted in lead 1 (fig. 1*A*).

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Case 2. A 60-year-old Negro man was admitted with a history of progressive congestive heart failure during the past 6 months. On physical examination there was an enlarged heart, basal rales, enlarged liver, and edema. Frequent premature beats were noted and the blood pressure was 120/80. The cause of the heart failure was not established but was assumed to be coronary disease. An electrocardiogram showed left ventricular hypertrophy, electric alternans in several precordial leads, digitalis effect and occasional main-stem extrasystoles (fig. 1*B*).

Case 3. A 34-year-old Negro woman was admitted with the chief complaint of left lower quadrant pain and tenderness. On examination a cervical erosion and uterine fibroids were found. An abdominal hysterectomy was performed and microscopy revealed endometrial hyperplasia. Three days after operation an arrhythmia was noted clinically and an electrocardiogram showed occasional main-stem and numerous ventricular premature beats (fig. 1*C*).

Case 4. A 48-year-old white man was admitted for excision of fissure in ano and repair of anal stricture. Blood pressure was 110/90 and there were no symptoms or signs of heart disease. A postoperative electrocardiogram, obtained because of the complaint of chest pain, was normal but contained numerous main-stem extrasystoles (fig. 2*A*). A second tracing, taken several days later, again revealed many main-stem extrasystoles (fig. 2*B*).

DISCUSSION

Main-stem extrasystoles evidently show remarkably varying degrees of prematurity. Some are barely premature so that they occur after the next expected sinus P wave (fig. 1*B*); others coincide with the P wave (fig. 2*A*); others are more premature with postincident P waves (fig. 1*A* and *C*); still others are so premature that they are interpolated (fig. 2*B*). Similar variability is observable in the examples previously published. In one case[7] the extra-

systolic focus in the main stem apparently acted as a parasystolic pacemaker.

The criteria considered necessary[1-3] for the diagnosis of main-stem extrasystoles are (1) premature beats having the same form as conducted sinus beats; (2) the sequence of P waves undisturbed in time and form; and (3) a compensatory pause following the extrasystole. Such beats thus have 1 feature in common with supraventricular and 2 in common with ventricular premature systoles. At times the sole manifestation of their presence is a shortening of the apparent P-R interval (e.g., fig. 1*B*, lead 3) and they are then especially likely to be overlooked.

TABLE 1.—*Relative Incidence of Various Types of Extrasystoles*

Type of extrasystole	Number of patients exhibiting extrasystoles	Per cent of total
Ventricular*	207	66.6
Atrial	81	26.0
Supraventricular†	11	3.5
A-V nodal	7	2.2
Main-stem	4	1.3
Sinus	1 (?)	0.3
	311	99.9

* Including ventricular extrasystoles occurring during atrial fibrillation, some of which presumably represent ventricular aberration in conducted beats.
† Of indeterminate origin.

It should be stressed that main-stem extrasystoles, even by these criteria which are the most rigid available, can never be diagnosed with unreserved certainty; for their diagnosis depends on the assumptions that beats originating in the atrioventricular node itself would be conducted backwards into the atria and that, as the beats in question are not so conducted, they are more likely to have arisen at a lower site above the branching of the bundle,

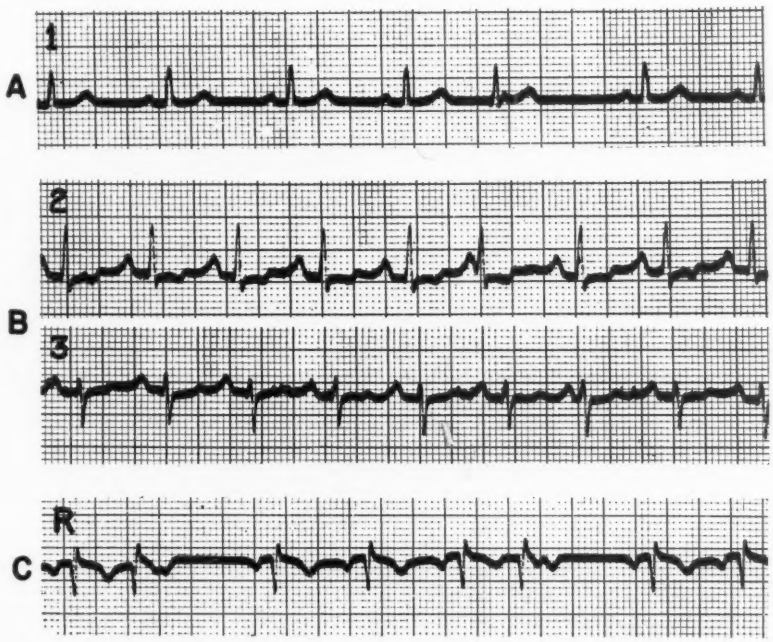

FIG. 1. *A*. Case 1. The fifth beat is premature and of supraventricular form, and is closely followed by a normal rhythmic P wave and a fully compensatory pause. *B*. Case 2. The sixth beat in lead II and the seventh in lead III are premature and of supraventricular form; in each lead the normal sinus P-wave sequence is undisturbed. *C*. Case 3. Second and sixth beats are premature and of supraventricular form; they are followed by undisturbed sinus P waves and compensatory pauses.

i.e., in the main stem. It follows that there can never be unassailable proof that a beat fulfilling the above criteria is not a *nodal beat with blocked retrograde conduction*. The extrasystoles published by Wenckebach and Winterberg[5] fully satisfy the criteria for main-stem extrasystoles but were regarded by them as nodal beats with retrograde block. By a similar token, however, the common ventricular extrasystole can also never be diagnosed with unequivocal certainty; for there is always the possibility that such a beat is a *main-stem extrasystole with aberrant ventricular conduction*. These reservations should be borne in mind in assessing any claims for the identification of main-stem extrasystoles.

Despite these limiting considerations, some authors have been satisfied with less than the criteria outlined above and, of the 7 records previously published, the claims of 2 may reasonably be questioned: 1. In the tracing of Lewis and Allen[4] the extrasystoles show ventricular aberration and therefore may well be ectopic ventricular systoles. 2. The record pub-

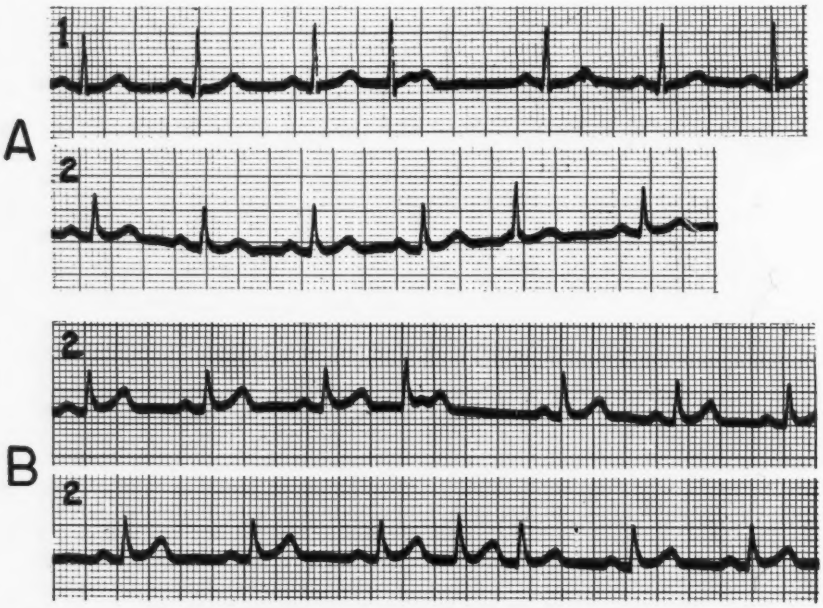

FIG. 2. Case 4. *A*. The fourth beat in lead I and the fifth in lead II are premature and of supraventricular form but do not disturb the normal P-wave sequence; in lead I the sinus P wave is seen deforming the S-T segment, in lead II it coincides with the premature QRS. Each beat is followed by a compensatory pause. *B*. Two strips from lead II at later date. The fourth beat in the upper strip is premature with a normal post-incident P wave deforming the S-T segment; the fourth beat in the lower strip is an interpolated extrasystole, presumably also arising from the main stem.

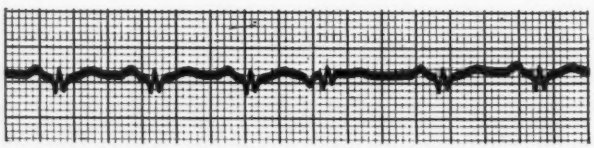

FIG. 3. The fourth beat is premature. Its P wave is obviously ectopic and presumably of nodal origin. This unequivocally supraventricular extrasystole is followed by a fully "compensatory" pause.

lished by Scherf and Schott[2] shows left bundle-branch block and the premature beat, regarded as a probable main-stem extrasystole, has the same configuration as the sinus beats. The P wave is not visible, however, and the diagnosis therefore rests heavily on the presence of a fully compensatory pause following the extrasystole. This is inadequate evidence on which to base the diagnosis, as it is not uncommon to observe a "compensatory" pause following an extrasystole that is unequivocally of supraventricular origin[8] (fig. 3).

Thus in the past 45 years apparently only 5 examples that satisfy the most rigid criteria for diagnosis have been published. As we have been able to observe 4 examples in a few months in a relatively small number of tracings, we believe that the phenomenon is probably not rare but often goes unrecognized.

Summary

Main-stem extrasystoles are stated to be very rare, yet, in the course of reading only 1,350 consecutive electrocardiograms, 4 examples were encountered—an incidence of 1 in less than 350 tracings. These 4 cases are briefly presented with illustrative electrocardiograms. The phenomenon is probably more overlooked than rare.

Summario in Interlingua

Extrasystoles a trunco major es considerate como multo rar. Tamen, in le curso del lecturas de solmente 1350 consecutive electrocardiogrammas, 4 exemplos de extrasystoles de iste genere esseva incontrate. Isto representa un incidentia de l in minus que 350 registrationes. Le 4 casos es discutite brevemente. Electrocardiogrammas illustrative es presentate. Il es probabile que le phenomeno es non-recognoscite plus tosto que rar.

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Medical Eponyms

By Robert W. Buck, M.D.

Angle of Louis. Johann Friedrich Conradi, in his Giessen Dissertation (1848) page 3, refers to the *angulus Ludovici* and in a footnote explains: "I understand by *angulus Ludovici* that more or less prominent outward angulation of the sternum which is formed by the junction of the manubrium with the body, and to the marked development of which, when the upper part of the thorax is sunken in, Louis of Paris has chiefly directed the attention of pathologists." No reference to the angle has been found in the published works of Pierre-Charles-Alexandre Louis (1787–1872).

Change in Relationship of Blood Volume to Weight in Congestive Heart Failure

By ROBERT K. FUNKHOUSER, M.D., WALTER H. PRITCHARD, M.D., AND ARTHUR S. LITTELL, SC.D.

Blood volume has been estimated in a small group of nonedematous hospitalized patients and in cardiac patients in severe congestive failure by both Cr^{51}-labeled red cells and iodinated (I^{131}) human serum albumin. In the analysis of the data attention is directed to a fallacy inherent in the usual ratio method of relating blood volume to weight. An alternative method of analysis is proposed that not only yields greater accuracy, but makes the analysis more sensitive. The authors present their interpretation of the effects of tissue wasting and accumulation of edema fluid on the changes in the relationship between blood volume and weight in congestive heart failure. Analyzing other data from the literature by this method the authors have demonstrated a relationship between the amount of edema fluid and the increase in blood volume in congestive failure.

ONE of the chief problems of evaluating the increases of the blood volume in congestive heart failure has been the choice of a suitable method for comparison of patients with failure and control patients.[1] In studies with human subjects it has not been possible to observe the "normal" blood volume of individuals before they acquire heart disease. The state of compensation reached following diuretics, salt restriction, and digitalis cannot be considered normal. Each subject's normal blood volume being lacking, it has been necessary to compare the blood volumes of the group of patients under study with the blood volumes of a group of normal or other control subjects.[2-4] Since there is among normal individuals a relationship between blood volume and size of the individual, the ratio of blood volume to weight (ml./Kg.) or to calculated surface area (L./M.^{2}) has frequently been used for this comparison. Tanner has pointed out that per-weight and per-surface area standards may lead to erroneous conclusions.[5] The earlier work in this field with dyes that label circulatory protein had shown greatly increased blood volume by means of the ratio method of analysis.[6-8] The results with radioactively labeled erythrocytes, however, have shown the blood volume elevated to a lesser extent if at all.[8-11] The purpose of this paper is to report the results of blood volume measurements in congestive heart failure by red cell and protein labeling and to demonstrate a more advantageous method of analysis than ratio comparisons when adjustment for body weight is desired.

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This work was supported by contributions from the Ferro Engineering Company and the Oglebay-Norton Company, Cleveland, Ohio.

METHODS

Selection of Patients

Of the 20 patients observed, 9 had been hospitalized for congestive heart failure. Eleven hospitalized patients, suffering from a variety of conditions not suspected to affect the blood volume, were chosen as a control group.

Each patient of the congestive failure group had edema and increased venous pressure, but the etiologic heart disease in each was believed to involve primarily the left heart. In addition, each person showed varying combinations of hepatomegaly, ascites, hydrothorax, cyanosis, increased circulation time, and cachexia, all indicators of serious disease. Two of the patients had received meralluride (Mercuhydrin) 3 and 12 hours before the study. Three of the failure patients were female whereas all of the control patients were male. Each of these 2 factors is recognized as an influence toward a lower average blood volume in the failure group.

In the control group about half suffered from chronic disease and the remainder were robust middle-aged men with coronary arteriosclerosis uncomplicated by heart failure.

Blood Volume Methods

Cr^{51}-Labeled Erythrocyte Method. The Cr^{51}-erythrocyte-labeling method of Gray and Sterling[12] was employed with minor modifications. The blood to be labeled was obtained from the subject, labeled, washed, and re-injected with a minimum of delay.

TABLE 1.—*Blood Volume Data of Control Group*

Initials, sex, age	Diagnosis	Wt. (Kg.)	Ht. (cm.)	S.A. (M^2)	Hct (%)	RV_{Cr}* (ml.)	PV_I* (ml.)	BV_{Cr}* (ml.)	BV_I* (ml.)	$BV_I - BV_{Cr}$
1. R. M., m, 82	Cerebral arteriosclerosis	53.7	166	1.58	42.8	1690	2610	3950	4560	610
2. K. N., m, 77	ASHD, hypertension	77.3	162	1.81	43.0	2190	3180	5080	5580	500
3. G. C., m, 44	ASHD, angina	70.1	172	1.81	43.8	1720	2600	3920	4630	710
4. L. C., m, 53	ASHD, angina, hypertension	79.4	170	1.90	48.0	2250	2850	4700	5480	780
5. G. Cu., m, 48	Myocardial infarct, conval.	82.2	180	2.00	46.3	2340	3190	5060	5940	880
6. E. Z., m, 55	ASHD, angina	72.6	164	1.77	45.8	1750	2340	3820	4320	500
7. G. M., m, 46	ASHD, angina	64.5	164	1.69	49.3	1710	2010	3470	3970	500
8. C. R., m, 72	Emphysema, pneumothorax	35.5	179	1.39	44.7	1400	2100	3120	3790	670
9. E. S., m, 53	? ASHD	77.3	175	1.91	44.5	2060	2810	4630	5060	430
10. O. S., m, 64	Cystitis, conval.	67.6	168	1.76	39.6	1990	3170	5020	5250	230
11. J. E., m, 48	Tabes dorsalis	50.3	164	1.52	43.2	1790	2830	4140	4980	840
Mean		66.4	169	1.74	44.6	1899	2699	4264	4869	
S.D.		14.4	6.3	.18	2.7	288	416	676	682	

* RV_{Cr}—Red cell volume estimated with Cr^{51}; PV_I—Plasma volume estimated with I^{131}; BV_{Cr}—Blood volume estimated with Cr^{51}; BV_I—Blood volume estimated with I^{131}.

The cells were washed once with sterile .9 per cent sodium chloride solution and resuspended for injection. Routinely, assays demonstrated that less than 1 per cent of the radioactivity in this suspension was in the suspending saline. An aliquot of the final suspension was used for the preparation of standards in duplicate.

Following the injection of approximately 100 μc. of Cr^{51} in a labeled cell suspension, blood samples were withdrawn without stasis from an indwelling no. 16- or no. 18-gage needle in an antecubital vein. The needle was kept patent with an obturator. The anticoagulant was dry heparin.

Following the injection of labeled cells in the opposite arm, 6 to 10 blood samples were drawn over a period of approximately 1 hour for determination of radioactivity. Since evidence was obtained that mixing was not entirely complete until about 25 minutes after injection, samples drawn earlier were not used in calculating the blood volumes. At least 5 samples of blood were used in each calculation of blood volume.

I^{131}-Labeled Human Serum Albumin Method. Commercially available I^{131}-labeled human serum albumin was used. The appropriate dilution was made so that each milliliter contained 10 μc. of I^{131}. With a 5-ml. Luer-lok syringe equal injections were made from the 4-ml. mark into a 1000-ml. volumetric flask and into an antecubital vein of the patient. The injection of I^{131}-labeled human serum albumin was made directly following the withdrawal of the last blood sample of the labeled cell procedure. Following the I^{131}-albumin injection, samples were withdrawn from the same indwelling needle as before at 10, 30, 50, and 70 minutes after injection. Plasma was assayed on all samples. Hematocrit values were determined on each blood sample counted, the blood being taken directly from the assayed tube after counting. Wintrobe tubes were spun at 2,000 G for 1 hour.

Assays of Radioactivity. Assays of radioactivity were carried out on samples of whole blood or plasma in the liquid state, with a conventional well-type scintillation counter, 3 ml. of fluid being contained in each sample.

RESULTS

The physical measurements and estimations of blood volume and its components are given for each subject in tables 1 and 2. The mean height for the control group was 169.4 cm. and for the failure group 170.8 cm. In spite of this similarity in height, the absolute mean red cell volume, plasma volume, and blood volumes by Cr^{51} cells and I^{131} albumin are higher in the congestive failure group than in the control group. In table 3 the probabilities that such different mean absolute values could have been obtained by chance are given in the first column. For each component of the blood volume the average of the failure group is significantly* greater than that of the control group.

* A probability value of .05 or less is taken as the criterion of significance in all statistical tests in this report.

TABLE 2.—*Blood Volume Data of Failure Group*

Initials, sex, age	Diagnosis	Wt. (Kg.)	Ht. (cm.)	S.A. ($M.^2$)	Hct (%)	RV_{Cr} (ml.)	PV_I (ml.)	BV_{Cr} (ml.)	BV_I (ml.)	$BV_I - BV_{Cr}$
1. C. M., m, 60	HCVD	67.1	172	1.78	40.3	2240	3650	5580	6100	520
2. C. H., m, 67	ASHD or HCVD	74.3	176	1.90	39.1	2220	4040	5670	6630	960
3. L. D., f, 38	RHD, pulmonary infarct	58.4	164	1.64	49.4	2070	2690	4200	5310	1110
4. M. J., f, 49	Aortic insufficiency	66.1	162	1.70	45.7	2130	3530	4670	6480	1810
5. P. S., m, 48	ASHD	75.8	166	1.82	51.8	2250	2760	4350	5730	1380
6. O. E., f, 58	HCVD	67.1	160	1.69	42.6	2370	3660	5560	6380	820
7. T. M., m, 47	ASHD or HCVD	140	179	2.50	35.6	3440	7580	9650	11760	2110
8. G. E., m, 53	RHD	77.6	174	1.91	44.6	2350	3550	5270	6400	1130
9. O. R., m, 38	ASHD	86.8	184	2.09	48.2	3360	4090	6970	7890	920
Mean		79.2	171	1.89	44.1	2492	3950	5769	6964	
S.D.		24.2	8	.27	5.3	515	1444	1678	1929	

TABLE 3.—*Comparison of Absolute Means and Mean Ratios of the Various Components of Blood Volume with Height, Weight, and Surface Area. The p Value Derived from a t Test is Given Below Each Pair of Means*

	Absolute ml.		÷ Height ml./cm.		÷ Weight ml./Kg.		÷ SA $ml./M.^2$	
	control	failure	control	failure	control	failure	control	failure
Blood volume Cr^{51}	4264	5769	25.16	33.50	66.06	73.12	2447	3001
	$p = .01$		$p = .01$		$p = .15$		$p = .003$	
Blood Volume I^{131} albumin	4869	6964	28.75	40.59	75.86	88.56	2801	3637
	$p = .003$		$p = .002$		$p = .03$		$p < .001$	
Red Cell volume Cr^{51}	1899	2492	11.21	14.52	29.35	32.17	1089	1311
	$p = .005$		$p = .002$		$p = .18$		$p < .001$	
Plasma volume I^{131} albumin	2699	3950	15.95	22.98	42.15	49.57	1555	2049
	$p = .01$		$p = .01$		$p = .05$		$p = .003$	
Plasma volume Cr^{51}	2365	3277	13.96	19.04	36.72	41.10	1361	1697
	$p = .03$		$p = .03$		$p = .20$		$p = .02$	

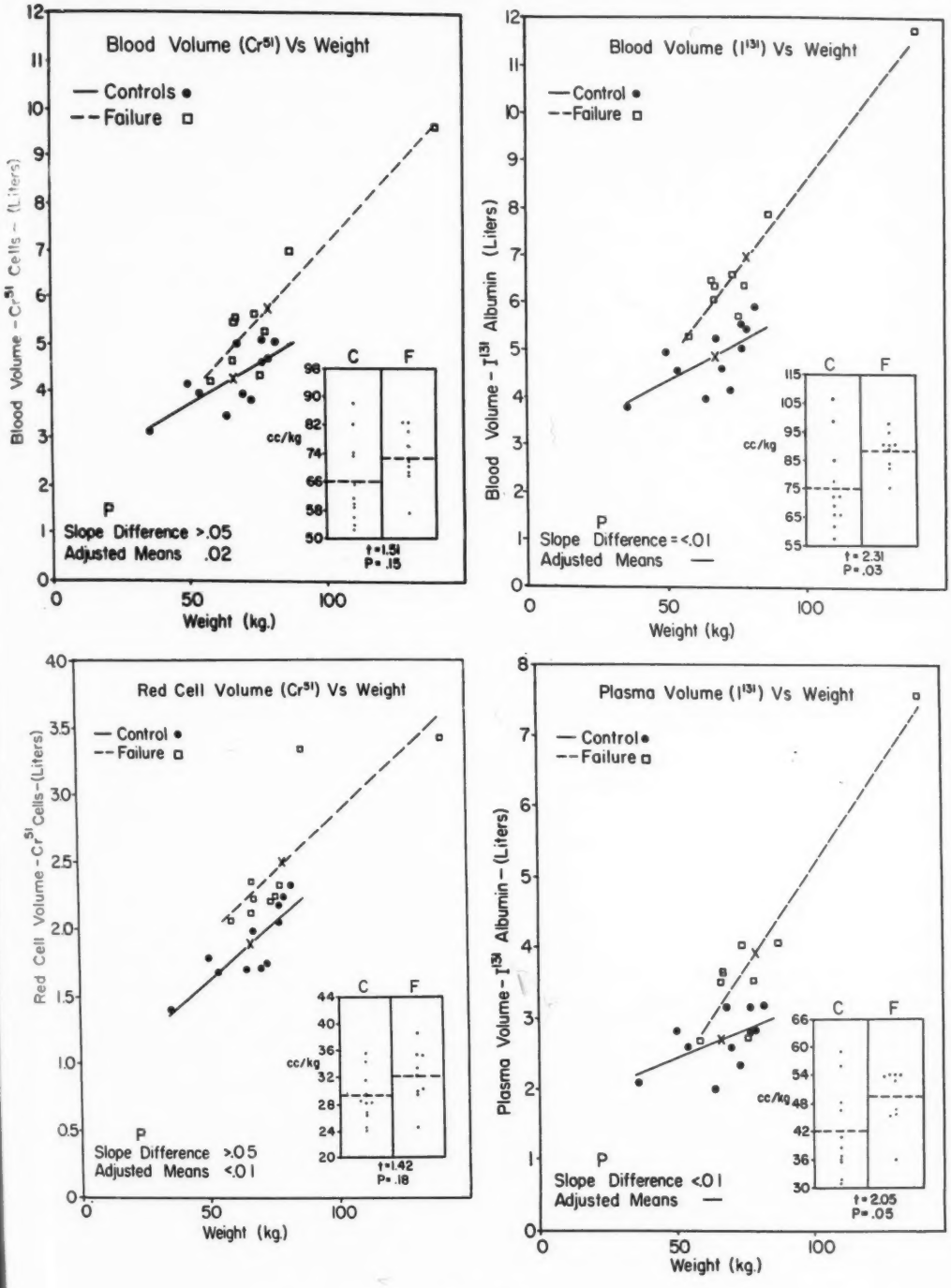
Since the distributions of weight and surface area of the 2 groups are different, in part because all of the patients with failure had edema, covariance analysis was applied to the data. A graph was made of the blood volume plotted against the weight for each control individual, and the points representing the subjects in failure were plotted on the same graph. If each set of points was described adequately by a straight line, it was assumed that the true relation, or regression of blood volume on weight, was linear. The least squares line was obtained for each group of individuals and the question was asked: "Are these lines 2 estimates of the

FIG. 1 *Top left.* Plot of blood volume by the Cr^{51} method against weight. The lines are least squares regressions among the points for control patients and patients with failure. The result of covariance analysis is given in the lower left corner. The diagram on the lower right shows ratio analysis of the same data. The horizontal dashed line in each group represents the mean. In spite of a significant difference in adjusted means, the ratio comparisons fail to show a significant difference.

FIG. 2 *Top right.* Plot of blood volume by the I^{131} method against weight.

FIG. 3 *Bottom left.* Plot of red cell volume by the Cr^{51} method. The failure regression is significantly higher than the control regression. The ratio comparisons on the lower right fail to show a significant difference.

FIG. 4 *Bottom right.* Plot of plasma volume by the I^{131} method against weight. In this instance both methods of analysis show a significant difference.


Blood Volume (Cr^{51}) Vs Weight
— Controls ●
-- Failure □
Blood Volume - Cr^{51} Cells - (Liters)
Weight (kg.)
P
Slope Difference >.05
Adjusted Means .02
C F
cc/kg
t=1.51
P=.15
Blood Volume (I^{131}) Vs Weight
— Control ●
-- Failure □
Blood Volume - I^{131} Albumin (Liters)
Weight (kg)
P
Slope Difference = <.01
Adjusted Means —
C F
cc/kg
t=2.31
P=.03
Red Cell Volume (Cr^{51}) Vs Weight
— Control ●
-- Failure □
Red Cell Volume - Cr^{51} Cells - (Liters)
Weight (kg.)
P
Slope Difference >.05
Adjusted Means <.01
C F
cc/kg
t=1.42
P=.18
Plasma Volume (I^{131}) Vs Weight
— Control ●
-- Failure □
Plasma Volume - I^{131} Albumin - (Liters)
Weight (kg.)
P
Slope Difference <.01
Adjusted Means —
C F
cc/kg
t=2.05
P=.05

FIGS. 1–4

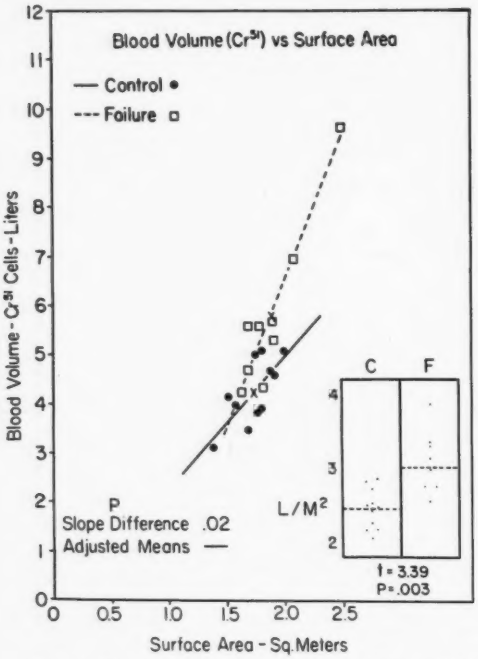


FIG. 5. Plot of blood volume by the Cr^{51} method against surface area.

same linear regression or may we conclude that they represent different regressions?" This question was answered by testing the significance of the difference between the slopes of the 2 lines. If the slopes were not significantly different, 2 parallel lines were fitted to the 2 sets of points and the vertical distance between the lines was tested. The vertical distance between these parallel lines represented the difference between the mean blood volumes of the 2 groups corrected or adjusted for differences in weight and was called the difference between the adjusted means.[13]

Our data have been plotted and subjected to covariance analysis. Figures 1–5 are representative graphs and are described below.

Blood Volume by Labeled Cells. The plot of the blood volume, as estimated by the dilution of Cr^{51}-labeled erythrocytes, against weight is given in figure 1. The solid line is the regression line for the control group; the broken line is the regression for the failure group. The points of the failure group fell mostly above the points of the control group but there was some mingling of the 2 sets. Since there was mingling of the 2 sets, it was not obvious that the relationship of blood volume to weight was truly different in the 2 groups. Statistical analysis showed that the slopes of these 2 lines were not significantly different, but that the difference between the adjusted means was significant ($p = .02$). Thus the relationships between the blood volume and weight were different in the 2 groups.

Blood Volume by I^{131}-Labeled Albumin. The covariance of blood volume as estimated by I^{131}-labeled human serum albumin with weight was also analyzed (fig. 2). The points of the failure group lie more strikingly above the controls in this instance than in figure 1. The difference in slopes of the 2 lines was significant ($p < .01$).

Red Cell Volume. The red cell volume as estimated by the dilution of Cr^{51}-labeled cells is plotted against the weight in figure 3. The slopes of the 2 lines were very similar, but the line for the failure group was significantly above that for the controls ($p < .01$, adjusted means).

Plasma Volume. The plasma volume as estimated by the dilution of I^{131}-labeled albumin was plotted against the weight in figure 4. The slopes were significantly different. The slopes were also significantly different when plasma volume as estimated with Cr^{51} erythrocytes was examined.

The relationships of blood volume, red cell volume, and plasma volume to surface area have also been examined by covariance analysis. In some instances the slopes were significantly different as, for example, in figure 5, which shows the relationship of blood volume as measured by labeled cells to surface area. In the others the difference between adjusted means was significant, with the points of the failure group lying above those of the control group.

Thus it was found that the blood volume as measured by erythrocyte dilution, by albumin dilution, and by addition of red cell volume to plasma volume was higher in the congestive failure group than in the control group. This was true whether these volumes were related to weight or to surface area.

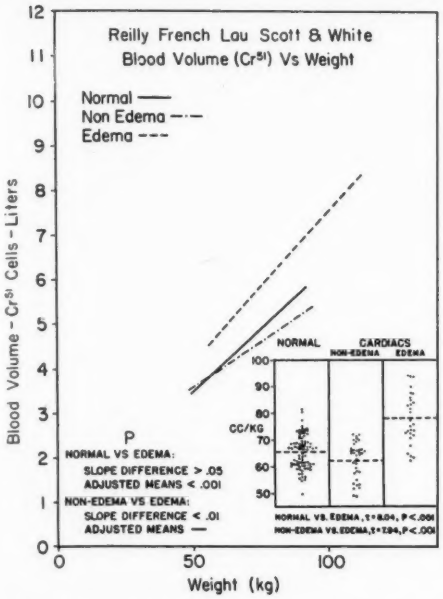


FIG. 6. Regression lines calculated from 89 normal subjects, and 37 nonedematous cardiac, and 29 edematous failure patients regrouped from Reilly and his co-workers.[9] Covariance analysis in this instance is in agreement with the conclusions of the authors, which were based on ratio analysis such as that illustrated on the lower right.

Analysis of the Data of Reilly, French, Lau, Scott, and White. Although this more sensitive method of analysis appeared to indicate a real increase in blood volume in congestive failure when applied to our small group, larger series of such data were sought for similar analysis. The only other set of data that was made available to us was that of Reilly et al.[9]

This much larger series of data was analyzed and is illustrated in figure 6. The blood volume as estimated with Cr^{51} erythrocytes is plotted against the weight. We have pooled their experimental data into 3 groups: (1) 89 normal subjects; (2) 37 patients with heart disease without peripheral edema (groups I, II, and III); and (3) 29 patients with heart disease with peripheral edema (groups IV and V). The result of covariance analysis supports their conclusion that the blood volume is elevated in patients with signs and symptoms of right ventricular failure. This is true whether the edematous cardiac patients are compared with nonedematous cardiac patients or with normal control subjects. *

DISCUSSION

Fallacy of Certain Ratio Standards. Blood volume data have usually been expressed as the ratio of the patient's blood volume to weight or to surface area.[14] Tanner[5] has emphasized the fallacy of using ratios unless it can be shown that the ratio of blood volume to weight or to surface area is constant over the full range of adult body size. Several investigators[15-17] have commented that the ratio of blood volume to weight is higher in small individuals than in large ones. If ratios proved constant over a large span of weight, a plot of blood volume against weight in a group of normal individuals would show points scattering about a line passing through the origin of the graph. But replotting of data from tables of "normal" adult blood volumes given in the literature[11, 18-24] shows that least squares regression lines of blood volume on weight pass considerably above the origin. In figure 7, line *A* represents a constant ratio of 70 ml./Kg., whereas line *B* is an idealized line based on available data; it demonstrates that in heavy persons the ratio of blood volume to weight is smaller than in lighter individuals.

Since the relationship between blood volume and weight in normal individuals is best expressed by a line that does *not* pass through the origin of the graph, a person's ratio does not indicate whether his point would be far above, close to, or far below the line.

Analysis of Our Data by Ratio Standards. The data of the present study may serve to illustrate the possible erroneous conclusions that might be drawn from ratio analysis. In the first column of table 3 the average values are compared and shown with the probability value derived from a t test. Similarly in the remaining columns, the means of ratios of volume to height, weight, and surface area are compared.

In each comparison in the table, the mean of the failure group is higher than that of the

* The authors of this work very kindly sent us a list of the individual red cell volumes, weights, heights, and hematocrit values of these 89 normal patients to make these calculations possible.

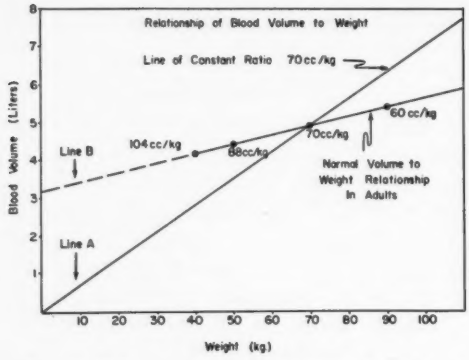


FIG. 7. Difference between the normal blood volume-weight relationship (line *B*) and the line of constant ratio (line *A*). Note different ratios exemplified along line *B*.

control group. In the ratio to weight column the difference in means is not significant for each of the volumes estimated with Cr^{51}. But in figures 1 and 3, a plot of the corresponding data indicates an increase in the blood volume in congestive failure.

Interpretation of Results of Regression Analysis in Congestive Failure. In congestive failure the body weight may be both increased by edema and diminished by tissue wasting. Let us consider the possibility that the increase in blood volume in congestive failure as shown in figure 1 was due to tissue wasting rather than to the formation of edema. The investigation of Keyes and his associates[24] of the effects of semistarvation in human beings sheds light on the effects of tissue wasting on blood volume. Their data indicate that there was an actual mean fall of 500 ml. in absolute blood volume during 24 weeks of semistarvation, even though the ratio of blood volume to weight rose. In figure 8 the least squares regression of blood volume on weight is given for their data obtained during the control period. The cross in this line represents the mean blood volume plotted against the mean weight. The closed circle to the left, lying on the dotted extension of the control line, is the mean blood volume and weight for the same individuals after semistarvation. It is apparent that the loss in blood volume and weight has been such that the pre-starvation blood volume-weight relationship has not been greatly disturbed. In the

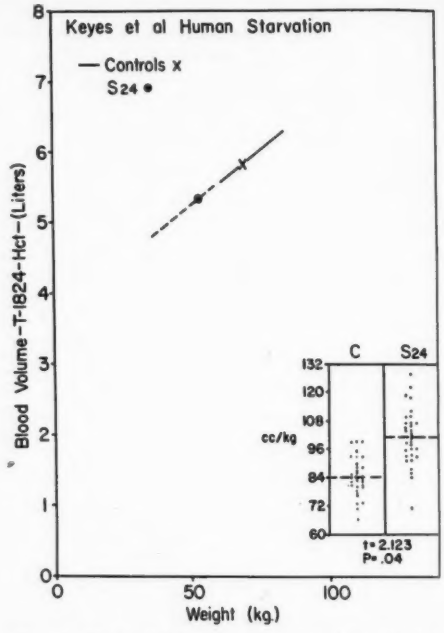


FIG. 8. The solid line is the regression calculated from control blood volume estimates, with the mean value represented by the cross. The dot representing the mean blood volume and weight after 24 weeks of semistarvation (S24) shows little departure from the control relationship. The ratio diagram gives a false impression of higher blood volume after semistarvation.

lower right corner of the figure, a striking and "significant" increase in the *ratio* of blood volume to weight in the same data is illustrated. This increase in the ratio should not be interpreted as indicating a rise in the blood volume during starvation. The authors of the work did not draw this erroneous conclusion. They were in a position to observe actual changes in blood volume in their subjects. Although neither of these 2 types of analysis is indicated in paired data such as these, in situations where different groups of individuals are used, ratios might lead to false conclusions.

Figure 9 illustrates our conception of the changes in the relationship of blood volume to weight in congestive heart failure. The heavy diagonal line represents the "normal" weight to volume slope as calculated from blood volume data in the literature. If blood volume decreases during the tissue wasting in conges-

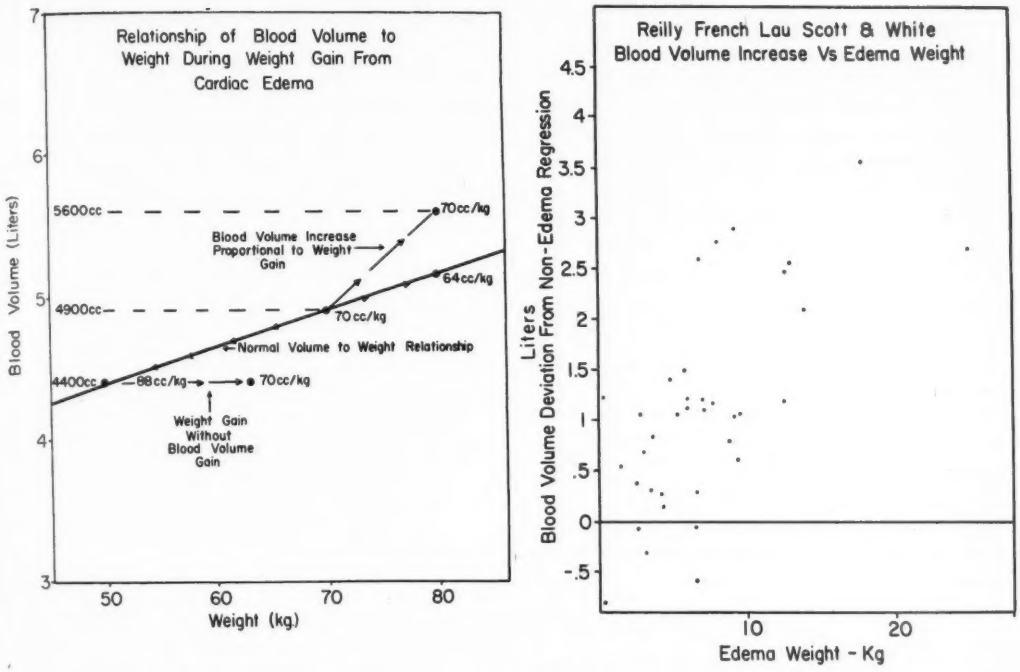


FIG. 9 *Left.* Diagrammatic representation of the mechanism of departure of the blood volume-weight relationship from the normal during congestive failure. Note the ratio of 70 ml./Kg. lying above, on, and below the normal relationship.

FIG. 10 *Right.* Note striking relationship between blood volume increase and the amount of edema.

tive heart failure as it does during semistarvation, the concurrent blood volume and weight change of the wasting individual may be represented by the movement of his point to the left along the diagonal. If an individual gains weight by accumulating edema without an increase in blood volume, his new point will move horizontally to the right as indicated by the lines and point "weight gain without blood volume gain." Such points will fall *below* this normal line.

On the other hand, if an individual gains weight from edema and his blood volume increases in a manner proportional to the slope of the normal volume-weight relationship, his new point will move up *along* the line to the right. Whenever weight gain is accompanied by an increase in blood volume of greater magnitude than this normal slope relationship, the point will fall *above* the diagonal line of normal relationship. It is important to note that weight gain may be accompanied by a blood volume increase of such proportions that if only ratios (ml./Kg.) were used, no change might be demonstrated. Again in figure 9 this is illustrated by "blood volume increase proportional to weight gain." Thus it can be seen from this figure that a person might have a "normal" ratio of 70 ml./Kg. yet have an actually decreased, normal, or increased blood volume with respect to the normal relationship that has been found to exist.

In order to assess a possible relationship between the amount of edema and the increase in blood volume in patients with congestive failure, further analysis was done. From the data of Reilly et al., the height of each edematous individual's point above the normal regression line was taken to represent an objective estimate of his gain in blood volume during failure. This estimated gain in blood volume was plotted against the amount of edema as

obtained from the difference between his "wet" and "dry" weights. The scatter of the points in figure 10 shows a relationship between blood volume increase and the amount of edema. Such a relationship has been postulated by many investigators interested in the mechanism of cardiac edema.

Since the loss of tissue substance in heart failure is probably associated in general with a decrease in the blood volume, and the gain of edema with an increase, the blood volume at any moment is likely to depend on the relative importance of these 2 factors in the particular instance under observation. In instances where the tissue loss has been great and the edema was slight, the blood volume might be lower than it was when the subject was in good health. When there has been greater modification of the weight by edema than by loss of tissue substance, the blood volume will usually be increased.

Summary

Blood volume data on a small series of patients in congestive heart failure have been presented in illustration of the importance of proper analysis of certain types of data. By using regression analysis, it was shown that the ability to detect significant differences in small groups is increased. Not only is the acuity of analysis increased, but possible erroneous conclusions may be avoided. In the analysis of data relating to congestive failure, it was shown that: blood volume is greater than normal and that the blood or plasma volume increase is related to the amount of edema.

Acknowledgment

The outstanding technical assistance of Miss Barbara Jambour is gratefully acknowledged.

Summario in Interlingua

Es presentate datos in re le volumine de sanguine in un parve serie de patientes con congestive disfallimento cardiac pro illustrar le importantia del appropriate analyse de certe typos de datos. Per le uso del analyse a regression il esseva monstrate que le detectibilitate de differentias significative in parve gruppos pote esser meliorate. Le acuitate del analyse es augmentate, e in plus le possibilitate de conclusiones erronee es evitate. In le analyse de datos relative a disfallimento congestive il esseva possibile monstrar que le volumine de sanguine es plus grande que normal e que le augmento del volumine de sanguine o de plasma es relationate al quantitate de edema.

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The human understanding when it has once adopted an opinion, either as being the received opinion or as being agreeable to itself, draws all things else to support and agree with it. And though there be a greater number and weight of instances to be found on the other side, yet these it either neglects and despises, or else by some distinction sets aside, and rejects; in order that by this great and pernicious predetermination the authority of its former conclusions may remain inviolate. And therefore it was a good answer that was made by the man who was shown hanging in a temple a picture of those who had paid their vows as having escaped shipwreck. They would have him say whether he did not now acknowledge the power of the gods—'Aye.' asked he again, 'but where are they painted that were drowned after their vows?'—FRANCIS BACON (1561–1626).

Electrocardiographic Diagnosis of Myocardial Infarction in the Presence of Left Bundle-Branch Block

By MYRON G. CHAPMAN, M.D., AND MORTON LEE PEARCE, M.D.

It is generally accepted that most myocardial infarctions are obscured on the electrocardiogram by left bundle-branch block. The number of published cases in which this could be evaluated, however, is small, and the case reports are scattered. We have studied 30 cases of myocardial infarction with left bundle-branch block in which the location of the infarction could be determined with certainty, by autopsy, or by a previous electrocardiogram with normal intraventricular conduction. Twenty such published cases have also been collected. Electrocardiographic abnormalities have been correlated with infarctions in different locations. The possible specificity of these abnormalities is discussed.

THE observation of Wilson and associates[1] that "in the presence of left bundle branch block it is seldom possible to make a diagnosis of myocardial infarction on the basis of electrocardiographic findings alone" is still widely accepted. A number of cases in which a myocardial infarction could be recognized in the presence of left bundle-branch block (LBBB) have been reported, but these usually have been single case reports, with the exception of the groups of cases reported by Dressler et al.[2] and by Sodi-Pallares and co-workers.[3, 4] Most of these have been diagnosed by Q waves in lead V_6, by S-T segment or T-wave abnormalities, or by fortuitous normally conducted complexes.

Our review of 50 cases of myocardial infarction with LBBB leads us to believe that a myocardial infarction produces electrocardiographic changes almost as often in the presence of LBBB as it does with normal intraventricular conduction. In most instances the presence of the myocardial infarction is indicated by changes in the QRS complex. As would be expected, the abnormalities of the QRS complex indicating the presence of a myocardial infarction are not always the same in the presence of LBBB as they are with normal intraventricular conduction. QRS configurations similar to those seen in our cases in association with myocardial infarction are also present in published cases. Several of these QRS abnormalities have not previously been described as being associated with myocardial infarction in the presence of LBBB.

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MATERIALS AND METHODS

We have studied all cases with complete LBBB in our files from 1953 through June 1956. Complete LBBB was diagnosed by the usual criteria. The QRS complex should be of 0.12 second duration or longer, of sinus origin, and associated with a P-R interval of at least 0.12 second. The left precordial leads should have a broad, slurred, or notched R wave with an abnormally delayed "intrinsicoid" deflection, similar complexes usually being present in lead I. There should be rS or QS complexes in lead V_1 with a normal "intrinsicoid" deflection. Cases in which the diagnosis of LBBB was questionable were excluded from this study, as were all cases of incomplete LBBB.

We have selected those cases in which the electrocardiogram could be evaluated by accepted criteria, such as autopsy data, a previous electrocardiogram with normal intraventricular conduction showing a myocardial infarction, or an electrocardiogram with intermittent LBBB. The electrocardiograms with intermittent LBBB had consecutive complexes with LBBB and normal intraventricular conduction. There were 30 cases of myocardial infarction with LBBB; the infarction was localized in 25 by autopsy, and in 5 by a previous electrocardiogram with normal intraventricular conduction. There were 13 cases with LBBB in which no gross infarct was found at autopsy. Five cases with intermittent LBBB were also studied.

In addition, the literature has been reviewed and all published cases of myocardial infarction with LBBB have been collected in which the location of the myocardial infarction was known—by autopsy or by normal intraventricular conduction. Inasmuch as the characteristic left precordial QRS complex is almost the *sine qua non* in the diagnosis of LBBB,

only those cases in which left precordial leads are available were included. Twenty such cases were found. Autopsy data were available in 13 of these cases. In 4 other cases, the infarction could be localized by a previous electrocardiogram with normal intraventricular conduction, and in the remaining 3 cases the infarction was localized by an electrocardiogram with normal intraventricular conduction shortly after the infarction had occurred.

Results

QRS Complex

Comparison of the configurations of the QRS complexes within each group of cases, classified by location of infarction, reveals certain similarities.*

Anteroseptal Infarction. Of the 17 cases with anteroseptal infarction, 4 cases had a Q wave in lead V_6 (fig. 1*B*), similar to cases previously reported. Three of these 4 cases were autopsied and extensive anteroseptal infarction was demonstrated in each. Of the 17 cases with anteroseptal infarction, there were Q waves in lead I in 6 cases and in lead aV_L in 10 cases. In our entire group of 43 cases, Q waves in leads I, aV_L, and V_6 were associated with anteroseptal infarction in every case except 1, in which there was a Q wave in lead aV_L only. Patchy myocardial fibrosis was present in this case.

Seven cases, in which there was moderately extensive infarction in the anteroseptal and apical regions, had an rsR′ in lead I, aV_L, or V_6 (figs. 2*C* and 3). The rsR′ configuration in these leads usually consisted of a small r wave, a small s wave extending just below the isoelectric line, followed by a tall R′. In some leads, there was apparent respiratory variation between an rsR′ and an R wave with a deep notch on the beginning of the upstroke that did not quite reach the isoelectric line. An rsR′ was frequently present in the same electrocardiogram with a Q wave in lead I, aV_L or V_6, or a notched S wave in lead V_4. The rsR′ was always associated with an anteroseptal infarction in this group of cases.

Every one of the 9 cases in which there was infarction of the anteroseptal and apical region

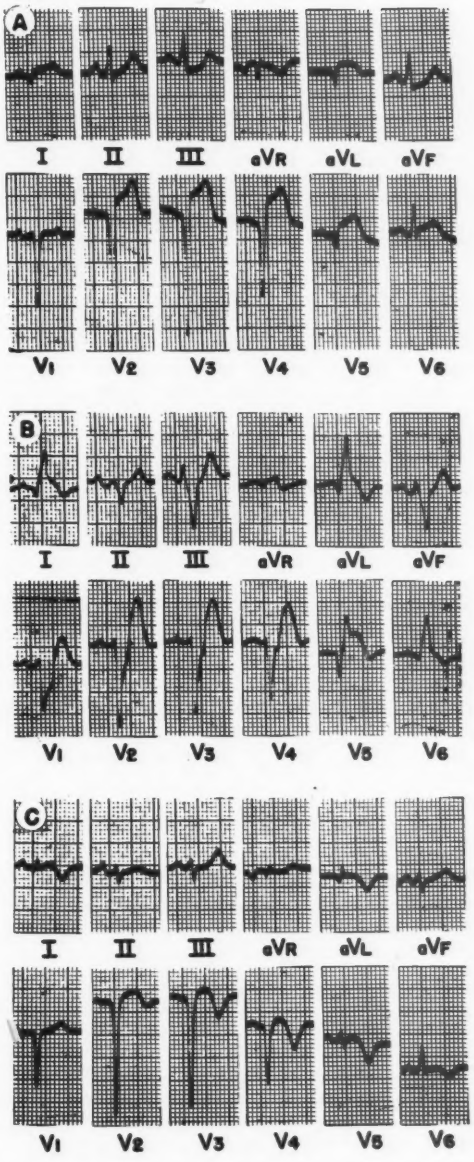

FIG. 1. Electrocardiograms of a patient with an acute anteroseptal myocardial infarction during normal intraventricular conduction (*A*), transient LBBB (*B*), and return to normal conduction (*C*). Note the Q waves and abnormally elevated S-T segments in leads I, aV_L, V_5, and V_6, and the abnormal precordial R progression in *B*.

* Mimeographed tables summarizing additional data on the cases are available from the authors on request.

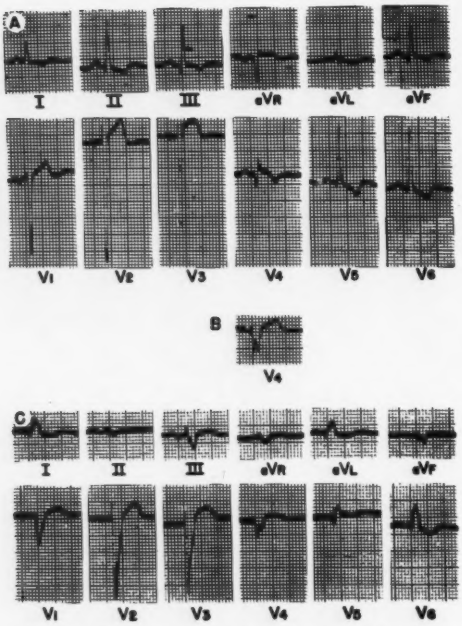

FIG. 2. Electrocardiograms of a patient with an old anterior infarction during normal conduction (*A*) and LBBB (*B*, *C*). Infarction of the septum and apex was also present at autopsy. Note the rsR′ in leads I, aV_L, V_5, and V_6 in *C*, and the notched S wave in lead V_4 in *B* and *C*.

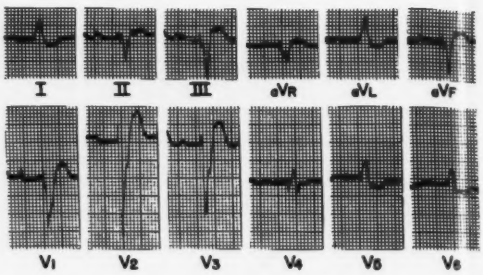

FIG. 3. Electrocardiogram of a patient with an old infarction of the entire septum and adjacent anterior wall of the left ventricle during LBBB. Note the rsR′ in lead V_5 and the initial notching of the S wave in lead aV_F. Autopsied.

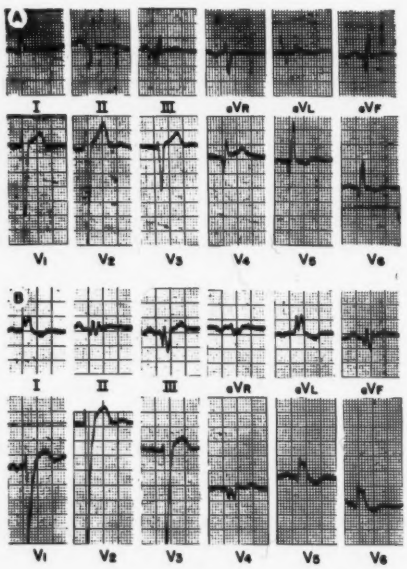

FIG. 4. Electrocardiograms of a patient with old anterior and posterior infarctions during normal conduction (*A*) and LBBB (*B*). Infarction of the septum and apex was also present at autopsy. Note the r′ in lead aV_F, the notched S wave in lead V_4, and the Q wave in leads V_5 and V_6 in *B*.

had early notching of the S wave or QS deflection in the precordial lead just to the right of the transition zone (figs. 2*C* and 4*B*). This notching is wide and deep, and is present in complexes of relatively small amplitude. It is usually on the downstroke of the S wave or QS deflection. It is to be distinguished from the fine notching at the tip of S waves with large amplitude that is present in some right precordial complexes. This notching begins at approximately 0.03 second after the beginning of the QRS complex in most cases. In a few cases it occurred after a longer interval following the beginning of the QRS but still occurred during the early part of the S wave. In our entire group of 43 cases there was only 1 case in which a configuration like this in V_4 was not associated with an anteroseptal infarction. This case also had patchy myocardial fibrosis.

In the group of 17 cases with anteroseptal infarction, 13 had a decrease in the height of the precordial R wave, going from right to left (figs. 1*B*, 2*C*, 3, and 4*B*). This decrease ranged from 0.5 to 4 mm., averaging 1.6 mm. It was present in every case in which the anteroseptal infarction was extensive. It occurred in only 1 of the 13 cases without infarction at autopsy. In every case in which there was an anteroseptal infarction, 1 or more of the following was

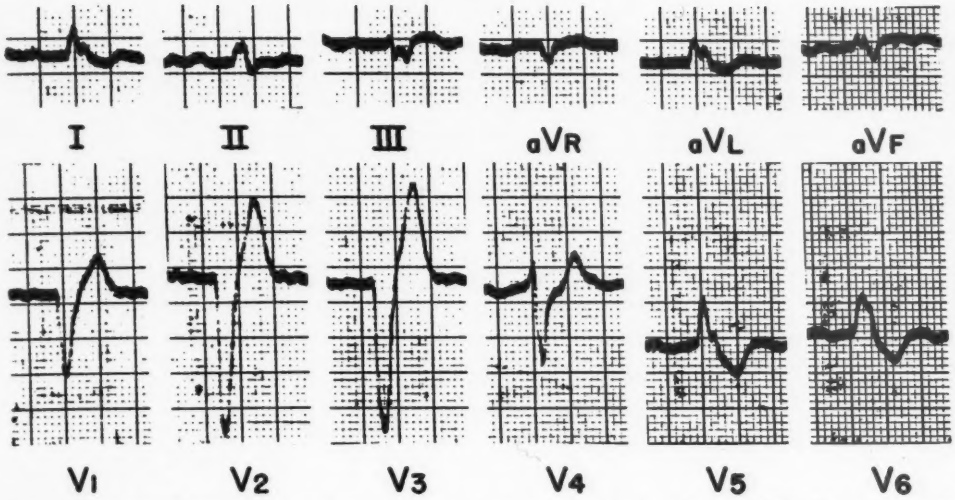

FIG. 5. Electrocardiogram of a patient with an old posterior infarction during LBBB. Note the notched r wave in lead aV_F. Autopsied.

present: a Q wave in lead I, aV_L, or V_6; an rsR′ in lead I, aV_L, or V_6; a notched S wave in lead V_4; or an abnormal precordial R progression.

Anterior Infarction. Of 3 cases with an infarction of the anterior wall of the left ventricle without septal involvement, 1 had an Rs in lead V_6. In the other 2 cases, in which the infarct was anterolateral, there was a decrease of 1 mm. in the height of the precordial R wave, going from right to left.

Posterior Infarction. Nine of the 10 cases with a posterior infarction had a notched R wave or an R′ in lead aV_F (figs. 4*B* and 5) and 8 of the 10 cases had a notched R wave or an R′ in lead III. A notched R wave in lead aV_F was present in 4 other cases in which a posterior infarction was not present. Patchy myocardial fibrosis was present in 2 of these cases. Patchy posterolateral fibrosis was present in a third case. In the fourth case, there was an old subendocardial infarct of the septum and lateral wall, and a vertical electrical axis.

Septal Infarction. Five cases had an infarction that predominantly involved the septum (figs. 3, 6*B*, and 7*B*). Each of these had initial notching of the S wave in lead aV_F. In each of these cases there was a large S wave or QS deflection in lead aV_F, with a small upward deflection during the early part of the S wave almost reaching the baseline. A complex similar to this was present in only 1 case without a septal infarct.

Other Cases. In our entire group of 43 cases, there were 5 cases in which QRS complexes similar to the ones described above were not associated with a transmural myocardial infarction. Gross patchy myocardial fibrosis was present in 3 of these 5 cases, and a subendocardial infarct and vertical electric axis were present in the fourth case. This case was the only one in the entire group with a vertical electric axis, all other cases having a horizontal axis. Neither infarction nor fibrosis was found in the fifth case.

A review of published cases of myocardial infarction with LBBB reveals most of them to be associated with QRS complexes similar to those described above. Twenty cases were found in which the location of the infarction was definitely known, by autopsy or by normal intraventricular conduction, and in which the electrocardiogram, with left precordial leads, was available for study.[2-11]

There were 13 cases with anteroseptal infarction and 2 cases with anterior infarction. Thirteen of these 15 cases had Q waves in lead I, aV_L, or V_6, an rsr′ in lead I or V_6, or a notched S wave in the precordial lead just to

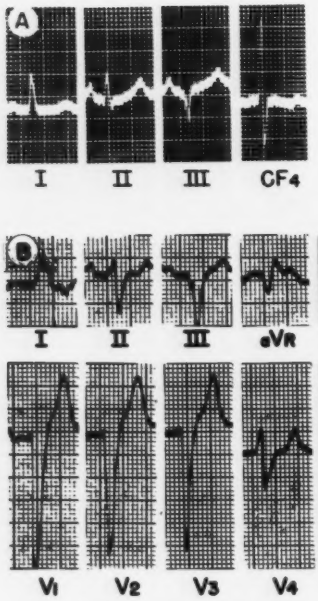

FIG. 6. Electrocardiograms of a patient with an acute infarction of the posterior septum (12-8-54) during LBBB (*B*). Note the initial notching of the S wave in lead aV_F in *B*. Autopsied.

the right of the transition zone, usually V_4. The other 2 cases not showing these QRS changes both had recent infarctions, one being 1 day old, the other being designated only as "recent."

In the group of 10 cases with posterior infarction there was a notched R wave or an R′ in lead aV_F or III in 5 of the 10 cases. Of the other 5 cases, lead aV_F was not available in 3, the septum was intact in 1, and both anterior and posterior infarctions were present in 3.

A number of other cases in the literature of myocardial infarction with LBBB that lacked 1 of the criteria for inclusion in this group also had 1 or more of the following complexes—a notched S wave in the precordial lead just to the right of the transition zone, an rsR′ in lead I, aV_L, or V_6, or a notched R wave or an R′ in lead aV_F or III. We have not found these complexes in published examples of uncomplicated LBBB or in our nonautopsied cases in which myocardial infarction has not been suspected clinically.

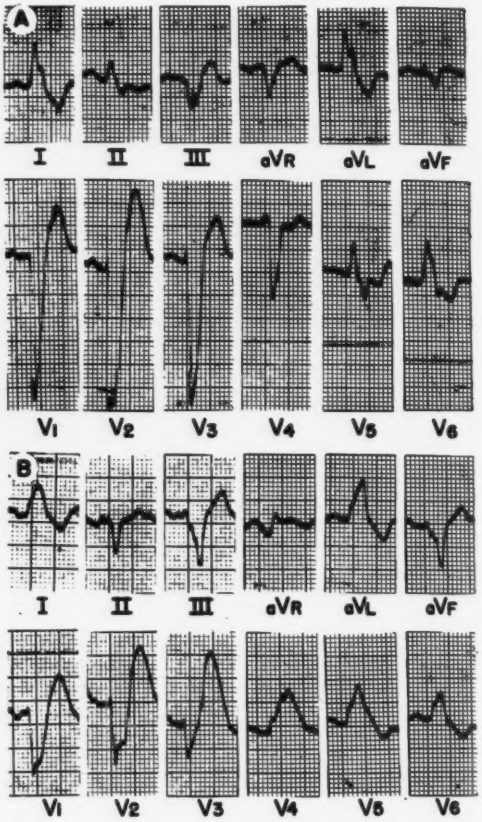

FIG. 7. Electrocardiograms of a patient with LBBB, prior to (*A*) and following (*B*) an acute infarction of the septum and adjacent anterior wall of the left ventricle. Note the marked elevation of the S-T segments in leads V_{2-5} in *B*. Autopsied.

The accuracy of these electrocardiographic features in indicating the presence of infarction in the combined group of 63 cases, 43 in our group and 20 from the literature, is shown in table 1. The first 4 electrocardiographic features, all associated with anteroseptal infarction, would appear to be a fairly reliable indication of anteroseptal infarction, in view of the number of cases available and the high degree of correlation. The electrocardiographic features apparently associated with posterior infarction may be causally related, or may be only coincidental. The correlation in the case of septal infarction is suggestive, but the num-

TABLE 1.—*Electrocardiographic Features of Myocardial Infarction with Left Bundle-Branch Block*

Location of Infarction	Electrocardiogram	Accuracy in 63 cases
Extensive anteroseptal	Q I, aV_L, V_6	38/39
Moderately extensive anteroseptal	rsR′ I, aV_L, V_6	10/11
	Notched S "V_4"	19/21
Anteroseptal	Abnormal precordial R progression	19/20
Posterior	R′ or notched R aV_F	11/16
Septal	Initial notching of S aV_F	5/6

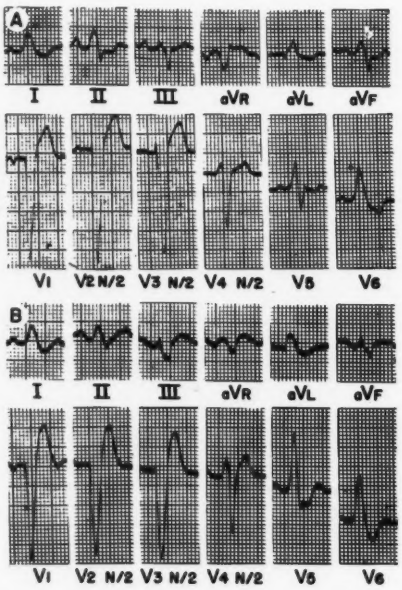

FIG. 8. Electrocardiograms of a patient with LBBB prior to (*A*) and during (*B*) an episode of coronary insufficiency. Note the marked elevation of the S-T junction in leads V_{1-3} in *B*. Autopsied.

ber of cases is insufficient at present to evaluate its reliability. Of the 8 cases in which a correlation similar to the above was not present, a myocardial infarction in another area was present in 3, patchy fibrosis was present in 3, and a vertical electric axis was present in 1.

S-T Segment and T Wave

Three cases with an acute anteroseptal infarction and LBBB were available. In the first

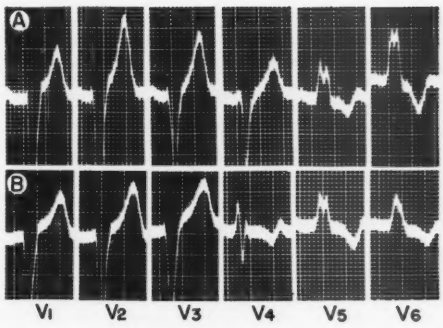

FIG. 9. Precordial electrocardiograms of a patient with LBBB, during (*A*) and following (*B*) an episode of coronary insufficiency. Note the pointed T waves of increased amplitude in *A*.

(fig. 7*B*), the electrocardiogram taken on the day of the infarction demonstrates marked elevation of the S-T segments in leads V_{2-5}, and an isoelectric S-T segment in leads I, aV_L, III, and aV_F, a change in comparison with a previous electrocardiogram with LBBB. In the second case (fig. 1*B*), an electrocardiogram taken on the day after the infarction shows marked elevation of the S-T segment in lead V_5, moderate elevation of the S-T segments in leads I, aV_L, V_{2-4}, and V_6, and depression of the S-T segments in leads III and aV_F. An electrocardiogram taken the day before, when normal intraventricular conduction was present, displays similar S-T segment abnormalities. In the third case, there is marked elevation of the S-T segments in leads V_{2-4} and an isoelectric S-T segment in lead I, a change from previous electrocardiograms.

Abnormal S-T segments were present in 2 cases with an anteroseptal and apical aneurysm. The S-T segments are abnormally elevated in leads V_{4-6} in the first case, and in leads V_{2-6} in the second case.

Electrocardiograms taken during a number of episodes of coronary insufficiency were available in 2 patients. A representative electrocardiogram of one is shown in figure 8*B*. There is elevation of the S-T junction in leads V_{1-4}, and depression in leads I, aV_L, V_5, and V_6. The T waves in leads V_{1-4} are tall and peaked, and the T waves in leads I and V_6 are diphasic. On each admission, this pattern

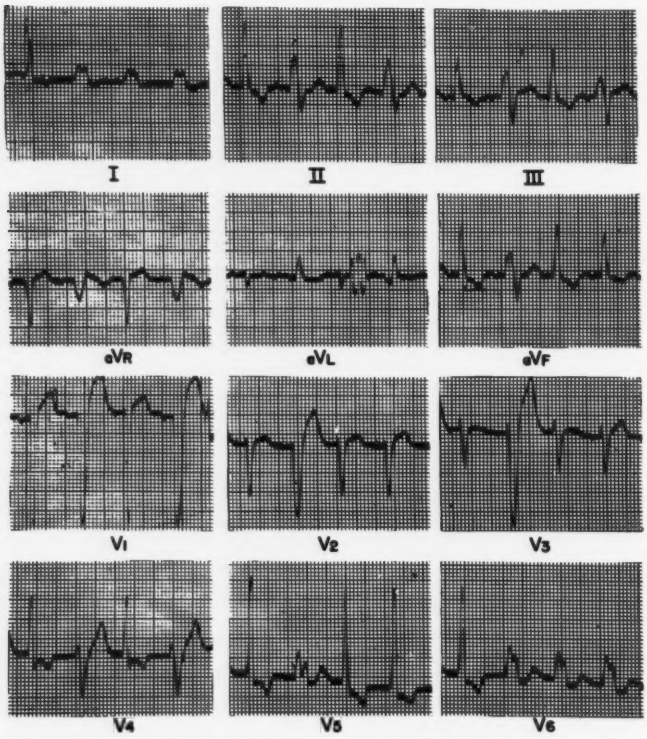

FIG. 10. Electrocardiogram of a patient with intermittent LBBB. He was taking digitalis. Note the abnormal T waves both with and without LBBB.

would soon revert to the usual pattern (fig. 8*A*). Similar changes in the T waves are seen in the other case (fig. 9). Figure 9*A* demonstrates the increased amplitude and more pointed T waves, most marked in leads V_{1-4}.

In the 5 cases of intermittent LBBB, there was no consistent correlation between the T-wave abnormalities present during normal intraventricular conduction and those present during LBBB. When abnormal T waves were present during normal intraventricular conduction, however, the most frequent changes in the T waves during LBBB were increased positivity of T waves in the precordial leads (fig. 10), and increased amplitude of T waves in the limb leads. The abnormal precordial T waves are taller and more pointed than normal in leads V_{1-4}, and usually diphasic, occasionally upright, in V_5 and V_6.

DISCUSSION

Wilson and his associates[1, 5, 6, 12-14] have discussed the diagnosis of myocardial infarction in the presence of LBBB in a number of papers. In 1936, Wilson[5] published a case of LBBB with QS complexes in leads V_5 and V_6, in which there was a large infarction of the anterior, posterior, and septal walls of the left ventricle. He considered that these QS complexes were due to the extensive infarction of the lower septum. In the study that summarized the experience of the Wilson group with the precordial electrocardiogram,[6] it is stated that S-T segment and T-wave changes may occur if the area of the QRS is small, and that an equiphasic RS in lead V_6 is suggestive of anterior infarction but is not a reliable sign. In 1944, Sodeman, Johnston, and Wilson[13] reported that in 8 autopsied cases of LBBB with a Q wave in lead I, 6 had infarcts, and 5 of these 6 had septal lesions.

Dressler, Roesler, and Schwager[2] in a review in 1950, presented and discussed 6 cases with definitely localized infarctions. They also summarized the electrocardiograms of appar-

ently uncomplicated LBBB in a study of 28 patients with no history of myocardial infarction or angina. In addition to the criteria previously mentioned for the diagnosis of infarction in the presence of LBBB, they observed a W-shaped QRS complex in lead II, which they felt was suggestive of a posterior infarction. They also presented definite criteria for S-T segment and T-wave configurations that are suggestive of infarction. Features considered suggestive of infarction include an isoelectric or elevated S-T junction following a prominent R deflection, a depressed or abnormally elevated S-T junction or a diphasic or inverted T wave following a deep S or QS deflection, and coronary T waves. (CR or CF leads were used in this study.)

Pantridge[15] in 1951 suggested that when an R wave was present in lead V_1, the diminution or disappearance of the R waves in leads V_{2-4}, in association with Q waves in the left precordial leads, is suggestive of anteroseptal infarction. He also suggested that atypical complexes in leads from the left side of the transition zone might be associated with infarction, a low primary peak of the R wave with anteroseptal infarction, and a low second peak with anterolateral infarction. He reported that the ventricular gradient was abnormal in each of 9 cases of LBBB with either grave myocardial disease or probable myocardial infarction.

In 1952, Sodi-Pallares, Rodriguez, and Bisteni[3, 4] discussed the problem of the electrocardiographic diagnosis of myocardial infarction complicated by LBBB, basing their conclusions on experience with clinical cases and experimental work on dogs. They concluded that recent infarctions are suggested mainly by abnormal S-T segments and abnormal T-wave configurations, and especially, by serial changes. In old infarctions, they found a qRs complex in the left precordial leads associated with infarction of the anterolateral wall and low septum in 2 cases.

Kert,[7] in 1952, presented a case of extensive anteroseptal infarction with Q waves in the left precordial leads. In 1953, Cabrera and Friedland[8] presented the results of a study of a group of 45 cases with LBBB. This group included only those cases in which there was notching or slurring in the final part of the QRS complex in precordial leads with an rS or QS configuration. They found a high degree of correlation between a late notch, 0.05 second or more in duration, in these leads and anteroseptal infarction. Fruscella and Boccardelli,[16] in 1954, found notching on both the downstroke and the upstroke of the S wave in similar leads in 10 cases of LBBB. Six of these cases had a clinical history of infarction. Kennamer and Prinzmetal,[17] in 1956, suggested that infarction may be suspected by the loss of voltage of the R wave in the left precordial leads when compared with a previous electrocardiogram. S-T segment and T-wave abnormalities were emphasized by Moia and Acevedo[18] and Somerville and Wood.[19] Master and co-workers[20] have found that 8 per cent of patients with acute myocardial infarction have LBBB.

Experimental work on dogs with myocardial infarction and LBBB has been done by Rosenbaum and his associates.[12] They concluded that when LBBB is present, infarction of the free wall of the left ventricle gives rise to no characteristic modification of the QRS complexes in the precordial leads. The location of the infarct in these dogs, however, on the anterior aspect of the apex, would make it probable that the anterior-inferior aspect of the septum was involved also. Examination of the published electrocardiograms reveals that there is present in the electrocardiograms of the dogs with an infarct a notched S wave in the precordial lead just to the right of the transition zone, corresponding to lead V_4 (point 8, dog 68; point 7, dog 70).[12] There is also an rsR′ in a position corresponding to lead V_6 (points 8 and 9, dog 70).[12] Similar complexes are present in the corresponding epicardial leads. Such complexes are not present in the precordial and epicardial electrocardiograms of the dog in which no infarction had been produced (fig. 7).[6] These complexes are the same ones we have found to be almost always associated with anteroseptal and apical infarctions in our cases. We have not found any published reports of the electrocardiographic study of experimentally produced posterior infarction in the presence of LBBB.

The reasoning leading to the belief that a

myocardial infarction can only rarely be diagnosed by the electrocardiogram in the presence of LBBB can be summarized as follows[6]:

> The presence of characteristic modifications of the QRS deflection in infarction almost always depends upon the transmission of the potential variations of the cavity of the left ventricle to the epicardial surface of the infarct and the adjacent parts of the body. . . . In left bundle branch block, the cavity of the left ventricle is positive at the beginning of the QRS interval, and, consequently, Q and QS waves do not occur in leads [taken over the infarct]. . . . When the septum is infarcted, as well as the free wall of the left ventricle, the cavity of the left ventricle is initially negative because the negativity of the cavity of the right is transmitted to it. Under these circumstances, the electrocardiogram may display large Q or QS deflections in leads from the left precordium.

This difficulty in the diagnosis of an isolated infarction of the free wall of the left ventricle has been extended by inference to the diagnosis of all other infarctions except one that destroys a large amount of septal myocardium and prevents the initial positivity of the left ventricular cavity. Clinically, however, an isolated infarction of the free wall, on which the generalization rests, is a relatively uncommon type of infarction. It was present in only 3 of our 30 cases of myocardial infarction with LBBB, while at least 20 of the 30 cases had infarction of the septum.

It is thought by many that the vector concept as applied in describing the origin of the changes in the QRS complex characteristic of infarction is more accurate than an interpretation in terms of cavity potential alone, called by some the "electric window" concept. In these terms, an infarction in the septum, in the presence of LBBB, may result in the loss of myocardium previously producing powerful[21, 22] early vectors. Various types of septal infarction—anterior or posterior, large or small—could cause various effects on the electrocardiogram.

Figure 1 demonstrates that the "cavity Q wave" associated with infarction is not always produced by cavity negativity alone. The Q waves present in leads $V_{2\text{-}4}$ in figure 1*A* would be interpreted in these terms as reflecting the cavity negativity that is transmitted through the electrically dead anteroseptal infarction. On the following day, however, in the presence of LBBB, r waves were present in leads $V_{1\text{-}4}$ (fig. 1*B*). Three days later, Q waves were again present in leads $V_{1\text{-}4}$ (fig. 1*C*). The r waves in leads $V_{1\text{-}4}$ during LBBB must have been produced by right ventricular forces. The "cavity Q wave" may be present over electrically functioning myocardium, therefore, when vectors produced by the part of heart directly under the lead are overbalanced by larger vectors with an opposite direction.

Among the other QRS features associated with infarction, the notching of the S wave in lead V_4, of the R wave in lead V_6, and of the S wave in lead aV_F have several characteristics in common. This notching is usually fairly close to the base line and it occurs during the early part of the QRS complex.

Wilson and Herrmann[23] have described the notching of the QRS that occurs in the normal electrocardiogram and in uncomplicated LBBB. In the former, notching usually was confined to the lead of smallest amplitude or occurred relatively close to the base line. In the latter, the notching was usually near the apex of the QRS in leads of large amplitude. They believed that these 2 types of notching differed entirely in their practical significance. The reasons for this belief can be summarized as follows[23]:

> The height of a deflection in a given lead at a given instant is dependent on two factors; the manifest potential difference (E) . . ., and the cosine of the angle between the direction in which this potential is developed and the line of lead. . . . The change in cosine per degree is much more rapid near 90 degrees than near zero degrees. Since, moreover, the deflection in a given lead is smallest when the electrical axis is perpendicular to the line of lead . . . , it follows that . . . the QRS of least amplitude will most faithfully record the changes in the direction of the vector E which occur during this interval. . . . Theoretically, notches may be produced by irregularities in the growth and decline of the manifest potential difference. . . . Such notches will be reproduced most faithfully in the QRS of greatest amplitude . . . It is probable that the notches which occur on the QRS group of [uncomplicated] bundle branch block curves are of this type.

In LBBB, these notches are a result of the sudden spread of activation through the left ventricle after its passage through the septum.[23]

In contrast to the notching in uncomplicated LBBB, due to irregularity in change of the manifest potential difference,[23] the notching of the QRS complexes that we have found to be associated with anteroseptal and septal infarction has the characteristics of the other type of notching, due to irregularity in the movement of the electric axis. The notching in our cases has occurred relatively close to the base line, and, the complexes in the precordial lead just to the right of the transition zone have been the complexes of least amplitude in the horizontal plane. They occur when the electric axis is relatively perpendicular to the line of that lead in contrast to the notching in uncomplicated LBBB that occurs when the electric axis is relatively parallel to the line of lead.

A second difference between the notching in these cases associated with anteroseptal and septal infarction and the notching in uncomplicated LBBB is the time of the notching during the QRS interval. The abnormal notch in the S wave in lead V_4 in our cases has begun approximately 0.03 second after the beginning of the QRS in most cases. The abnormal notch in the rsR′ complexes has begun approximately 0.02 second after the beginning of the QRS. In LBBB the first upstroke of the R wave in lead V_6, which is due to activation of the septum, is usually 0.05 to 0.06 second in duration. In the dog, where activation of the heart does not take as long as in the human, the time required for the wave of activation to cross the septum in LBBB has been experimentally measured to be from 0.03 to 0.04 second.[21, 24] The abnormal configurations described above, therefore, are produced during the advance of the wave of activation through the septum and, possibly, during the early part of the activation of the adjacent free wall. The notching at the apex of the R wave in lead V_6 in uncomplicated LBBB, on the other hand, usually occurred 0.05 second or more after the onset of the QRS.

Although it was anticipated that this early notching of the S wave in the precordial lead just to the right of the transition zone might be produced in a "transitional" complex, such a complex could not be found in cases of uncomplicated LBBB. An extensive precordial exploration in a group of 8 such cases, each with a broad, notched R wave in lead V_6, did not reveal early notching of the S wave in any lead near the transition zone. The appearance of this notching for the first time after anteroseptal infarction in 2 cases, and its presence only in dogs with infarction[12] also tend to identify the notching with infarction.

The decrease in height of the precordial R wave in going from right to left would appear to be due to loss of anteroseptal myocardium that had previously been producing early positive potential in the midprecordial leads. The slight decrease in height of the precordial R waves in the 2 cases with anterolateral infarction in our group may or may not be due to the infarction.

It would appear, therefore, that the Q wave and the rsR′ in leads I, aV_L, and V_6, the early notching of the S wave in the precordial lead just to the right of the transition zone, and the abnormal precordial R progression are all a result of the same process—infarction of myocardium in the anteroseptal area, the Q wave being produced by large infarctions, and the rsR′ and the notched S V_4 being produced by smaller infarctions. The downward deflection on the early part of the upstroke of the R wave, producing the rsR′ configuration, appears to have a significance similar to that of a Q wave. It could be called a "delayed Q wave," delayed by the time necessary for passage of the wave of activation through the septum before it reaches the infarcted area.

The association of the early notching of the S wave in lead aV_F with septal infarction in most cases raises the possibility that a septal infarction that is totally obscured during normal intraventricular conduction might produce recognizable changes on the electrocardiogram during LBBB. The difference in the patterns of activation in the 2 situations lends support to this possibility. During normal intraventricular conduction, the septal vector is much smaller than the left ventricular vector present at the same time. The loss of this septal vector by infarction produces little change in the resultant total vector. During LBBB, however, the septal vector is much larger dur-

ing the early part of the QRS complex than the right ventricular vector also present. In this situation, it is possible that septal infarction could produce diagnostic changes on the electrocardiogram.

The findings in posterior infarction appear to be of a more heterogeneous nature, possibly due to the wider anatomic distribution of infarcts that are included in this classification. The notch in the R wave in leads III and aV_F may also have the significance of a Q wave in some cases.

The group of 13 cases without gross infarction cannot be regarded as a normal control group, as 12 of the 13 had myocardial fibrosis and 9 of the 13 had a history of congestive failure. It may be that the fibrosis in these cases was extensive enough to alter the sequence of activation, producing these patterns. Burch[25] has observed that even a small amount of fibrosis can cause a recognizable change in the electrocardiogram. He found that septal fibrosis was present frequently in cases in which Q waves were absent in leads I, V_5, and V_6, during otherwise normal intraventricular conduction. In a series of 95 autopsied cases of diffuse, patchy myocardial fibrosis in the absence of confluent infarction, Weinberg and co-workers[26] found a progressive increase in slurring and decrease in voltage of the QRS complexes to be correlated with such lesions. This was found in 5 of his 8 cases with bundle-branch block.

Q waves in leads V_5 and V_6 with a late "intrinsicoid" deflection could be produced either by an anterolateral infarction with a so-called peri-infarction block[27] or a block involving one of the major subdivisions of the left bundle, or by an extensive anteroseptal infarction with LBBB. We believe that the cases presented here with Q waves in leads V_5 and V_6 are cases with LBBB, because each one was associated with an anteroseptal, rather than anterolateral, infarction. It should be mentioned that a Q wave in leads I, aV_L, or V_6 during LBBB may not be necessarily indicative of infarction, as suggested by the case presented by Lapin and Sprague,[28] in which a Q wave was present in these leads only during inspiration. There was no clinical evidence of a myocardial infarction in their patient.

Although the correlation of the QRS features described above with myocardial infarction has appeared to be high in this group of cases, 63 cases is not a large number for statistical purposes when they are broken down into several categories. Furthermore, the QRS changes in lead aV_F that appear to occur with the predominantly septal and posterior infarcts are of a minor character, and occur in only a few leads. When the R′ and notched R wave in lead aV_F are used as an indication of posterior infarction, there are a large number of "false positives;" this feature, especially, needs to be evaluated further. More extensive correlation of electrocardiographic changes with clinical and autopsy findings is necessary before these electrocardiographic features can be applied with confidence in the diagnosis of myocardial infarction. Further experimental studies are in order also, to place these findings on a sound basis. It should also be remembered that with LBBB, as without it, a myocardial infarction may occur without apparent change of the electrocardiogram.

Another electrocardiographic pattern, the "LBBB with precordial leads that erroneously suggest a RBBB," has been presented by Sodi-Pallares and Rodriguez[3] and by Richman and Wolff[29] as being due to a particular type of myocardial infarction with LBBB. Sodi-Pallares and Rodriguez suggested that this pattern was produced by infarction of the anterolateral wall and moderately extensive infarction of the septum, while Richman and Wolff suggested that it was produced by infarction of the septum and of the lateral and diaphragmatic walls of the left ventricle. The question of whether either type of infarction can change the precordial leads in LBBB to resemble those in RBBB, would appear to require experimental demonstration.

Although it has been stated[1] that characteristic changes in the S-T segment and T wave are usually obscured by the alterations of the T complex produced by the conduction defect except when the area of the QRS is small, each of the 3 cases in which electrocardiograms were taken during the acute stage of a myocardial

infarction has marked S-T segment elevation (figs. 1*B* and 7*B*). The area of the QRS complex in each of these cases was fairly large. These few cases would suggest, therefore, that characteristic S-T segment elevations may be present during LBBB in cases with acute myocardial infarction, even when the area of the QRS is fairly large. The S-T segment changes that we have observed have been similar to those described by Dressler and co-workers[2] and Sodi-Pallares and associates.[3, 4] It is of interest to note the close similarity between the complexes with marked S-T segment elevation in leads V_4 and V_5 in figure 7 during acute anteroseptal infarction in the presence of LBBB (fig. 7*B*), and the electrocardiograms from epicardial leads taken by Kennamer and Prinzmetal[17] 2 minutes after ligation of a branch of the anterior descending coronary artery in a dog with LBBB.

Although the apparent abnormalities noted in the T wave may be the result of an abnormal ventricular gradient, little reliance can be placed on these changes alone, in view of the many causes of T-wave abnormalities. Sodeman[30] has observed that diphasic or upright T waves in lead I are not necessarily abnormal in LBBB. We also have observed many instances of slight terminal positivity of the T waves in leads I, aV_L, and V_6 in cases not suspected of myocardial damage.

Although not related directly to LBBB, it should also be mentioned that a myocardial infarction can be diagnosed occasionally when, in the presence of LBBB, there is a postextrasystolic beat with normal intraventricular conduction.[5] Infarction has also been suspected by the occurrence of premature beats "of the 'intermediate type,' that is, due to excitations which activate the 2 ventricles in normal sequence because of suitable site of ventricular focus."[2]

Summary

A study of the electrocardiograms of 50 patients with myocardial infarction and left bundle-branch block (LBBB) reveals that QRS changes that appear to be characteristic of myocardial infarction are present in many such cases.

Extensive anteroseptal infarction in the presence of LBBB is associated with Q waves in leads I, aV_L, and V_6, and an abnormal precordial R progression. When the infarction is less extensive, rsR′ complexes are present in the same leads, and the S wave or QS deflection in the precordial lead just to the right of the transition zone, usually V_4, is deeply notched. One or more of these findings were present in each of the 17 cases of anteroseptal infarction in our group. The notching of the early part of the upstroke of the R wave in left precordial leads producing an rsR′ complex, would appear to be the equivalent of a "delayed Q wave," in its significance in indicating anteroseptal infarction.

Anterior infarction without septal involvement was present in 3 cases in our group, 1 case having an Rs configuration in lead V_6, and the other 2 having an abnormal precordial R progression.

Nine of the 10 cases with posterior infarction in our group were associated with a notched R wave or an R′ in lead aV_F. A similar configuration was present in lead III in 8 of the 10 cases.

Each of 5 cases with predominantly septal infarction in our group was associated with initial notching of the S wave in lead aV_F.

Similar complexes were present in most cases collected from the literature, and in published examples of the electrocardiograms of dogs with myocardial infarction and LBBB.

The electrocardiograms of several cases demonstrate that the "cavity Q wave" does not always reflect pure cavity negativity. Theoretic reasons, clinical experience, and experimental data are discussed that suggest that the early notching of the R wave in leads I, aV_L, and V_6, and of the S wave in leads aV_F and V_4, are different from the usual notching in uncomplicated LBBB, and are related to myocardial infarction.

Abnormal elevation of the S-T segment was present in leads I, aV_L, and in the precordial leads in each of the 3 cases of acute anteroseptal infarction in the group. S-T segments were also abnormally elevated in the precordial leads in 2 cases with an anteroseptal and apical

aneurysm. These S-T segment elevations appear to have the same significance during LBBB as they have during normal intraventricular conduction. No consistent correlation of T-wave changes with ischemia could be demonstrated.

Further clinical, autopsy, and experimental evaluation is necessary before these findings can be applied with confidence in the diagnosis of myocardial infarction.

Addendum

Since completion of this paper, 8 additional autopsied cases of myocardial infarction with LBBB have been studied, with findings similar to those reported above. Since completion also, the English edition of Demetrio Sodi-Palleres' book *New Bases of Electrocardiography*, has become available. He discusses the problem of the electrocardiographic diagnosis of myocardial infarction in the presence of LBBB and emphasizes that in the case of septal infarcts, LBBB actually aids in the detection of the infarct. His experimental work is summarized in the book and several new clinical cases are presented.

Summario in Interlingua

Le studio del electrocardiogrammas de 50 patientes con infarcimento myocardial e bloco de branca sinistre ha revelate que alterationes de QRS, apparentemente characteristic de infarcimento myocardial es presente in multe tal casos.

Extense infarcimento anteroseptal in le presentia de bloco de branca sinistre es associate con undas Q in le derivationes I, aV_L, e V_6 e un anormal progression de R precordial. Quando le infarcimento es minus extense, complexos rsR′ es presente in le mesme derivationes, e le unda S o le deflexion de QS in le derivation precordial justo al dextera del zona de transition (usualmente V_4) es profundemente indentate. Un o plures de iste aspectos esseva presente in cata un del 17 casos de infarcimento anteroseptal in nostre gruppo. Le indentation del prime parte del ascendita del unda R in derivationes sinistroprecordial producente un complexo rsR′ pare esser le equivalente de un "retardate unda Q" in su qualitate de indication de un infarcimento anteroseptal.

Infarcimento anterior sin implication septal esseva presente in 3 casos de nostre gruppo. Un de iste casos habeva un configuration Rs in derivation V_6, e le altere 2 habeva un anormal progression de R precordial.

Nove del 10 casos con infarcimento posterior in nostre gruppo esseva associate con un indentate unda R o un R′ in le derivation aV_F. Un simile configuration esseva presente in derivation III in 8 del 10 casos.

Omne le 5 casos con infarcimento predominantemente septal in nostre gruppo esseva associate con indentation initial del unda S in le derivation aV_F.

Simile complexos esseva presente in le majoritate del casos colligite in le litteratura e in publicate specimens de electrocardiogrammas de canes con infarcimento myocardial e bloco de branca sinistre.

Le electrocardiogrammas de plure casos demonstra que le "unda Q a cavitate" non reflecte semper un pur negativitate de cavitate. Rationes theoric, experientias clinic, e datos experimental es discutite que indica que le indentation al initio del unda R in derivationes I, aV_L, e V_6 e del unda S in derivationes aV_F e V_4 non es identic con le indentation usual in non-complicate bloco de branca sinistre sed es relationate con infarcimento myocardial.

Anormal elevationes del segmento S-T esseva presente in derivationes I, aV_L, e le derivationes precordial in omne le 3 casos de acute infarcimento anteroseptal in nostre gruppo. Le segmentos S-T esseva etiam anormalmente elevate in le derivationes precordial in 2 casos con aneurysma anteroseptal e apical. Iste elevationes del segmento S-T pare haber le mesme signification in bloco de branca sinistre como in normal conduction intraventricular. Nulle correlation uniforme inter alterationes de unda T e ischemia poteva esser demonstrate.

Additional evalutationes clinic, necroptic, e experimental es necessari ante que iste constatationes pote esser applicate con confidentia al diagnose de infarcimento myocardial.

Acknowledgment

The authors wish to express their appreciation to Dr. Franklin D. Johnston and Dr. Morley J. Kert for reviewing this material.

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A Clinical Study of the Brachial Arterial Pulse Form

With Special Reference to the Diagnosis of Aortic Valvular Disease

By ERNEST W. HANCOCK, M.D., AND WALTER H. ABELMANN, M.D.

A survey was made of the clinical usefulness of pulse forms from direct brachial arterial puncture of 250 patients. A prolonged duration of systolic upstroke and an anacrotic notch were found in most instances of severe aortic stenosis, but also frequently in patients with insignificant degrees of aortic stenosis, and occasionally in normal subjects. Characteristic, but nondiagnostic changes in the pulse form were noted in aortic insufficiency, mitral insufficiency, anemia, hyperthyroidism and exercise. The diagnostic significance of these findings is discussed.

THE recording of the arterial pressure pulse by direct puncture of the brachial artery has become a routine procedure in clinical cardiac physiology. In the diagnosis of aortic stenosis, particularly, the arterial pulse tracing has been considered of diagnostic importance. The pulse contour has been used in recent years to confirm the clinical diagnosis of aortic stenosis,[1, 2] to assist in the selection of patients for surgical treatment of aortic stenosis,[3] and to evaluate the results of aortic commissurotomy.[4] The characteristic abnormalities of the pulse in aortic stenosis have been considered to be a prolonged duration of the systolic upstroke, an anacrotic notch, low systolic and diastolic pressures, and a narrow pulse pressure. These features have long been known to the clinician, and were described and illustrated in detail with externally recorded sphygmograms a generation ago.[5, 6] There have also been extensive studies in experimental animals,[7-11] demonstrating in addition a prolonged duration of systole in aortic stenosis and a lesser degree of transformation of the arterial pulse contour in the course of transmission to the periphery. They have also suggested that the degree of alteration of the pulse form is related to the degree of the aortic stenosis. It is upon these experimental studies, in addition to the older clinical observations, that present-day interpretation of arterial pulse contours is largely based.

However, published material on direct human arterial pulse contours has been scant and fragmentary. There is a need for a more complete description of the contours observed clinically in normal and abnormal states. This paper is directed at that purpose, being a review of brachial artery pressure tracings from 250 patients taken during the past 4 years, with particular attention to the problem of exact diagnosis of aortic valve lesions.

MATERIAL AND METHODS

Direct brachial arterial pressure tracings were obtained in the following manner. A needle of 18 gage or larger was inserted percutaneously into the brachial artery in the antecubital space under local anesthesia, with the patient lying recumbent. The needle was connected by a rigid tubing up to 6 feet in length to an electromanometer (Sanborn) or strain-gage manometer (Statham P23A), and the tracing was recorded with appropriate amplifiers on a direct-writing oscillograph (Sanborn) at a paper speed of 25 mm. per second. Mean pressure was obtained by electric damping.

Artifacts and damping due to small clots in the needle, air bubbles or leaks in the connecting system, failure of the needle tip to lie free in the artery lumen, or improper angulation of the arm were eliminated by appropriate adjustments; an excessively damped normal tracing may be indistinguishable from the characteristic abnormal tracing of aortic stenosis. If there was not a free arterial flow from the needle, or if the pulse contour was not reproducible after repeated flushing of the recording system, then the validity of the tracing was questioned. Damped tracings were not included in the study.

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This work was supported in part by a grant from the U. S. Public Health Service.

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Dr. Abelmann is an Established Investigator of the American Heart Association.

Exercise was performed on a bicycle ergometer in 81 cases.

Cardiac output in the normal subjects was determined by the dye dilution technic.

On each tracing, the systolic, diastolic, and mean pressures, the pulse pressure, the systolic upstroke duration, the duration of "systole," the slope of the systolic upstroke, and the cycle length were measured. The duration of the systolic upstroke was taken as the time interval from the beginning of the systolic rise to the point of peak systolic pressure. "Systole" was defined as the time interval from the beginning of the systolic rise to the lowest point of the dicrotic notch, or to the point of abrupt change in rate of decline of the downstroke. The slope of the upstroke was measured as the rate of rise in pressure, in mm. Hg per 0.01 second over the steepest unbroken portion of the upstroke, usually the initial portion. The time measurements were usually accurate to the nearest 0.01 second, although some flattened or rounded pulse contours were difficult to measure accurately. The physiologic variation of cycle length, upstroke duration, and "systole" was usually at least 0.01 second in a continuous tracing over a short period of time, and greater than this when measured at different times.

From the total number of 250 patients, data from the pulse tracings of 106, constituted into 6 groups, are presented in detail. Patients not presented in detail included 56 with aortic valve lesions not verified by left heart catheterization, operation, or autopsy, 20 with mitral stenosis, 52 with alcoholism and cirrhosis of the liver, and 16 with miscellaneous conditions.

Group 1 consists of 40 "*normal subjects*," of whom 6 were healthy house officers and 34 were convalescent patients from the wards of the Boston City Hospital. All were selected as control subjects for one or another cardiovascular or pulmonary study on the basis of showing no evidence of cardiovascular or pulmonary disease by clinical examination, electrocardiogram, chest roentgenogram or fluoroscopy. On the basis of age, this group is subdivided into group 1A, including 20 subjects ranging from 20 to 37 years of age, mean 27.1 years, and group 1B, including 20 subjects ranging from 38 to 84 years of age, mean 48.1 years.

Group 2 consists of 20 patients with *aortic stenosis, proved severe*, and represents a consecutive series of such patients from whom satisfactory brachial artery pressure tracings were available. All had typical clinical evidence of aortic stenosis with significant symptoms, and were under consideration for aortic valve surgery. Eight who had left heart catheterization had calculated valve areas in the range of 0.4 to 0.9 cm.^{2} Seventeen who were operated upon for aortic stenosis were estimated at the time of operation to have valve areas in the range of 0.4 to 0.5 cm.^{2} by direct transaortic palpation or, in 4 cases, by the passage of transventricular dilators. Fifteen of the operated patients showed systolic pressure gradients in excess of 50 mm. Hg across the aortic valve as determined by direct measurement at the time of operation. The 3 unoperated patients all came to autopsy and were found to have severe aortic stenosis, the valve orifice not admitting a fingertip, and judged to be in the range of 0.4 to 0.6 cm.^{2}

Four patients in this group showed evidence of some aortic insufficiency in the form of moderate or loud aortic diastolic murmurs and significant dilatation of the left ventricle, with diastolic blood pressures ranging from 45 to 83 mm. Hg (G. V., M. S., J. B., A. L.). It was thought in each case, after clinical study and palpation of the valve at operation, that predominant stenosis was present, with a degree of associated insufficiency impossible to measure with present methods, but evidently much less than "free" aortic insufficiency.

Group 3 consists of 13 patients with *aortic stenosis, proved not severe*. These patients were seen during the same period of time as those of group 2. All had typical clinical evidence of aortic stenosis and were under serious consideration for aortic valve operation, but were eventually judged to have no functionally significant narrowing of the valve. In 7, this conclusion was based on the finding at the time of operation of less than 10 mm. Hg pressure gradient across the aortic valve in systole. In 5 it was based on the finding at left heart catheterization of a left ventricular systolic pressure no higher than the brachial artery systolic pressure, and in 1 patient on the appearance of the aortic valve at autopsy, the valve being normal except for some sclerotic thickening of the leaflets, but associated with severe coronary artery disease.

Group 4 includes 20 patients with what was termed "*myocardial failure*." These patients presented various degrees of congestive heart failure, attributed clinically to nonvalvular heart disease, usually hypertensive or coronary heart disease. None was thought to have high output failure.

Group 5 consists of 6 patients with the clinical picture of "free" *aortic insufficiency*, with seriously progressive signs of left ventricular failure, all subsequently shown at autopsy to have the expected pure aortic insufficiency without stenosis or other valvular disease.

Group 6 consists of 7 patients with severe rheumatic *mitral insufficiency* without stenosis. The absence of stenosis was proved at autopsy in 5, and was considered clinically evident in the other 2 (R. S., S. P.). All had marked cardiac enlargement, atrial fibrillation, and chronic congestive heart failure.

Results

Data from groups 1–6 are given in table 1, and estimates of the statistical significance of the differences are presented in table 2.

TABLE 1.*—*Quantitative Data of Pulse Tracings*

	Age	Systolic	Diastolic	Mean	PP	Upstroke	Systole	R-R	Slope
Group 1									
Mean	37.6	125.0	72.3	94.1	52.7	0.112	0.283	0.818	8.94
S.D.	13.6	34.1	7.55	2.8	9.4	0.039	0.033	0.128	4.39
C.V.	36.2	27.2	10.4	2.98	17.8	35.3	11.6	15.6	49.1
Group 1A									
Mean	27.1	118.0	68.8	86.6	49.0	0.094	0.283	0.814	8.5
S.D.	5.3	8.6	5.3	6.7	7.6	0.031	0.037	0.126	4.3
C.V.	19.5	7.2	7.7	7.8	15.5	32.0	13.1	15.4	48.5
Group 1B									
Mean	48.1	131.1	74.2	96.9	56.4	0.129	0.282	0.821	9.3
S.D.	11.0	15.5	9.4	12.3	10.2	0.040	0.033	0.139	6.0
C.V.	22.8	11.8	12.6	12.7	18.1	31.2	11.7	16.9	64.5
Group 2									
Mean	49.9	120.0	65.0	86.5	52.5	0.201	0.33	0.786	5.01
S.D.	8.10	19.5	8.1	8.7	19.7	0.03	0.08	0.03	1.70
C.V.	16.2	16.3	12.5	10.1	37.5	14.9	24.8	3.9	33.9
Group 3									
Mean	46.8	140.0	74.2	97.2	65.8	0.171	0.307	0.801	6.56
S.D.	8.22	37.6	11.0	17.1	34.7	0.027	0.037	0.138	2.93
C.V.	17.5	26.8	14.9	17.6	52.7	10.9	12.2	17.3	45.2
Group 4									
Mean	59.7	156.2	82.6	106.2	73.7	0.111	0.331	0.846	11.72
S.D.	12.3	10.3	6.0	5.8	7.5	0.013	0.140	0.197	8.11
C.V.	20.6	6.6	7.3	5.5	10.2	11.5	48.2	23.3	69.1
Group 5									
Mean	42.3	157.5	39.5	83.3	98.0	0.098	0.287	0.742	23.5
S.D.	19.8	10.8	17.3	17.1	72.5	0.043	0.010	0.082	14.9
C.V.	46.9	6.9	43.4	20.5	74.0	43.5	3.47	11.0	62.6
Group 6									
Mean	35.3	120.9	67.1	85.7	53.7	0.079	0.230	0.774	14.10
S.D.	15.1	25.9	12.4	13.3	18.6	0.080	0.039	0.136	11.53
C.V.	43.0	21.2	18.5	15.5	34.7	100.1	16.9	17.6	81.8

* In this and other tables, BP = systolic and diastolic pressure in mm. Hg; mean pressure is in mm. Hg; PP = pulse pressure in mm. Hg; upstroke = duration of the systolic upstroke in seconds; systole = duration from the beginning of the systolic rise to the dicrotic notch, in seconds; R-R = cycle length, in seconds; slope = steepest slope of the upstroke, in mm. Hg per 0.01 second; S.D. = standard deviation; C.V. = coefficient of variation, in per cent.

TABLE 2.—*Significance of the Differences of the Mean Values*

Groups	Age	Systolic	Diastolic	Mean	PP	Upstroke	Systole	R-R	Slope
1A–1B	*7.7*	*3.3*	*2.24*	*3.3*	*2.62*	*3.1*	0.14	0.18	0.28
1 –1B	*3.8*	1.0	0.8	1.04	1.36	1.64	0.08	0.16	0.04
1–2	*4.6*	0.72	1.1	1.2	0.01	*9.7*	*2.3*	0.50	*2.18*
1B–2	0.56	*2.03*	*3.34*	*3.12*	0.78	*6.3*	1.1	*3.16*	1.30
1B–3	0.45	0.82	0.00	0.06	0.99	*3.7*	0.41	0.96	0.76
1B–4	*3.7*	*6.05*	*3.37*	*3.01*	*6.1*	1.95	0.73	1.05	1.50
2–3	0.93	1.8	1.4	1.4	0.78	*2.96*	1.03	0.64	0.60
3–4	*3.4*	1.3	1.6	1.86	0.81	*5.0*	0.75	0.67	1.64
2–4	*3.0*	*4.3*	*2.5*	*4.7*	1.5	*7.7*	0.27	1.09	*7.90*

This table presents the ratios of the observed differences between the means of the 2 groups for each measurement to the standard error of the difference between the means. If the observed difference is more than twice the standard error of the means, then there is a less than 5 per cent probability that the 2 groups represent random samples from the same population, i.e., $p = <0.05$. If the ratio is 2.50, then $p = <0.0125$, and if the ratio is 3.00, then $p = <0.003$.[23]

Normal Subjects (group 1, fig. 1)

The systolic upstroke duration in 40 normal subjects ranged from 0.06 to 0.20 second, with a mean value of 0.11 second. The upstroke duration was the most variable of the measurements. There was considerable variation in the details of the pulse forms (fig. 1); anacrotic (J. Sh., A. My.) and bisferiens (R. Mo.) forms were encountered. Comparison of the mean values of groups 1A and 1B showed that, as a group, the older normal subjects had significantly higher systolic, diastolic, and mean pressures, wider pulse pressures, and longer upstroke durations than the younger normal subjects. The slope of the upstroke was a highly variable measurement, and did not differ significantly between the younger and older groups of normal subjects. Thus, the

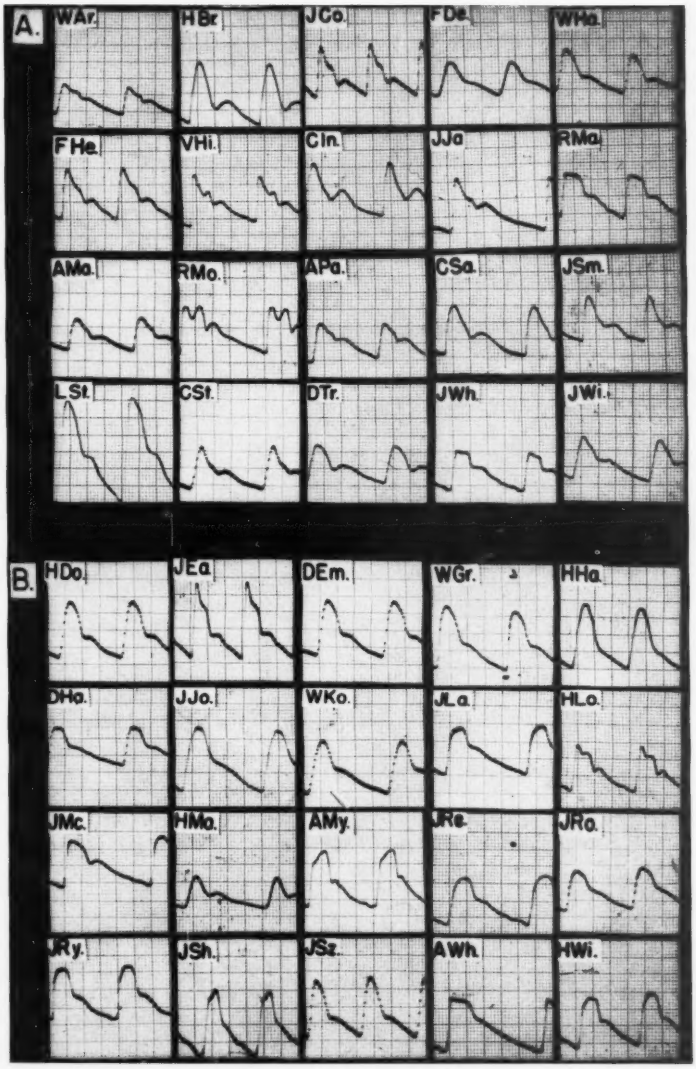

FIG. 1. *A*. Brachial arterial pulse forms of 20 normal subjects, ages 20 to 37 years (group 1A). *B*. Brachial arterial pulse forms of 20 normal subjects, age 38 to 84 years (group 1B). In this and other illustrations, the vertical scales in mm.Hg are not identical. All illustrations have an identical horizontal time scale, each heavy vertical line signifying 0.20 second.

highly significant difference in upstroke duration was predominantly due to the tendency of the pulse contours of older patients to show a gradually rounded peak instead of a sharp early peak as was characteristic of the pulse contour of almost all younger normal subjects.

The length of the cardiac cycle was not related to the upstroke duration in either group of normal subjects.

Aortic Stenosis, Severe (group 2, fig. 2A)

The upstroke duration in these patients ranged from 0.14 to 0.24 second, with a mean value of 0.20 second. The range overlapped that of the normal subjects to a mild degree (fig. 3), but the difference between the means was highly significant ($p = <0.01$). The patients with aortic stenosis also showed significantly lower systolic, diastolic, and mean pressures, and slower heart rates than the normal subjects of comparable age (group 1B), although the total group of normal subjects taken together differed significantly from the aortic stenosis group only in the duration of the systolic upstroke. The mean pulse pressure in the aortic stenosis group was smaller than that of group 1B, but the difference was not statistically significant. This finding documents a fact now widely recognized clinically; that a narrow pulse pressure is a characteristic feature in only a small minority of cases of severe aortic stenosis. The pulse pressure cannot be relied

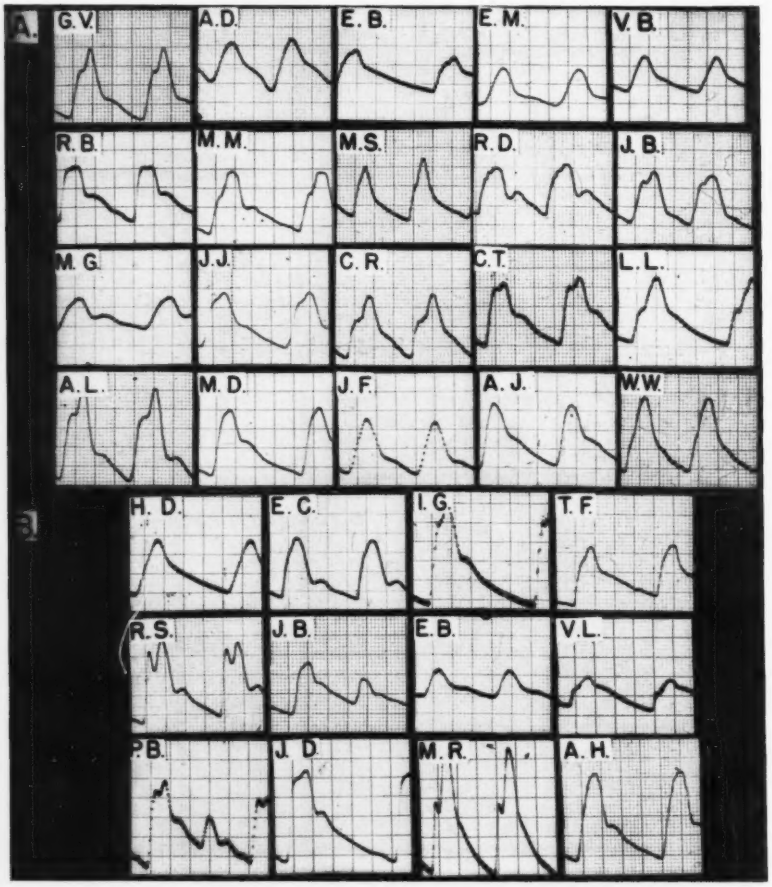

FIG. 2. *A*. Brachial arterial pulse forms from 20 patients with proved severe aortic stenosis (group 2). *B*. Brachial arterial pulse forms from 12 patients with aortic stenosis proved not severe (group 3).

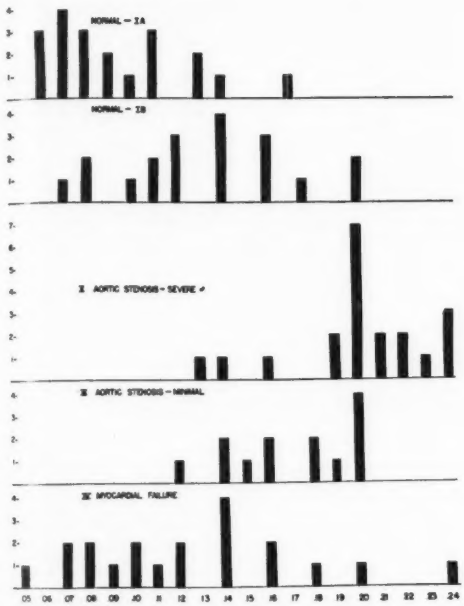

FIG. 3. Frequency distribution of the duration of the systolic upstroke (*abscissa*, seconds) in groups 1 to 4 (*ordinate*, number of patients).

upon as a guide to the severity of aortic stenosis.

The significant prolongation of "systole" and the more gradual slope of the upstroke in aortic stenosis as compared with the total group of normal subjects ($p = <0.05$) are more likely due to factors related to age than to factors related to aortic stenosis, because there was no significant difference in these measurements between groups 2 and 1B, which are of comparable age. The prolonged upstroke, then, appeared to be the most characteristic abnormality of the arterial pulse form in aortic stenosis.

The abnormal pulse form that appeared to be most typical was that with an upstroke duration of 0.20 second or longer, and a distinct notch rather low on the anacrotic limb (cf. C. R., M. M., L. L.). This pattern was not seen in any patient without aortic stenosis. On the other hand, in some instances of severe isolated aortic stenosis there was no anacrotic notch.

The Valsalva maneuver often exaggerated the anacrotic notch during the initial cycles of the first phase, and occasionally during the overshoot, or sometimes brought out the appearance of an anacrotic notch where there had been little or none in the resting tracing (fig. 4*E*). One normal subject showed some degree of this change, however, and it has not always been present in severe aortic stenosis.

Aortic Stenosis, Not Severe (group 3, fig. 2B)

In group 3 the pulse forms resembled closely those of group 2. The systolic upstroke duration ranged from 0.12 to 0.20 second, mean 0.17 second. There was considerable overlap with normal subjects, and with the severe aortic stenosis group, sufficient to render diagnosis of an individual case unreliable on the basis of this measurement alone (fig. 3). However, the mean upstroke duration was significantly longer than that of the normal group and significantly shorter than that of the aortic stenosis group. None of the other measurements differed significantly from those of normal subjects of comparable age, nor from those of cases of severe aortic stenosis. These results support the idea that aortic stenosis not only leads to prolongation of the systolic upstroke, but that such prolongation actually is related in degree to the degree of valve narrowing, as suggested by experimental observations, but not yet proved in man.

In both groups 2 and 3, there was evidence of a direct relation between stroke volume and upstroke duration in individual patients. This was evident in plotting cycle length against duration of upstroke in patients with atrial fibrillation, and also in patients with frequent ventricular extrasystoles, in which case the large beat following a compensatory pause tended to show a longer upstroke and more prominent anacrotic notch than the resting pulse form.

Myocardial Failure (group 4)

This group showed a mean age of 59.7 years, significantly older than the other groups. Compared with group 1B, mean age 48.1 years, these patients with "myocardial failure" showed significantly higher systolic, diastolic, and mean pressures, and wider pulse pressures. The group included 5 patients with definite hypertension, greater than 200 mm. Hg systolic,

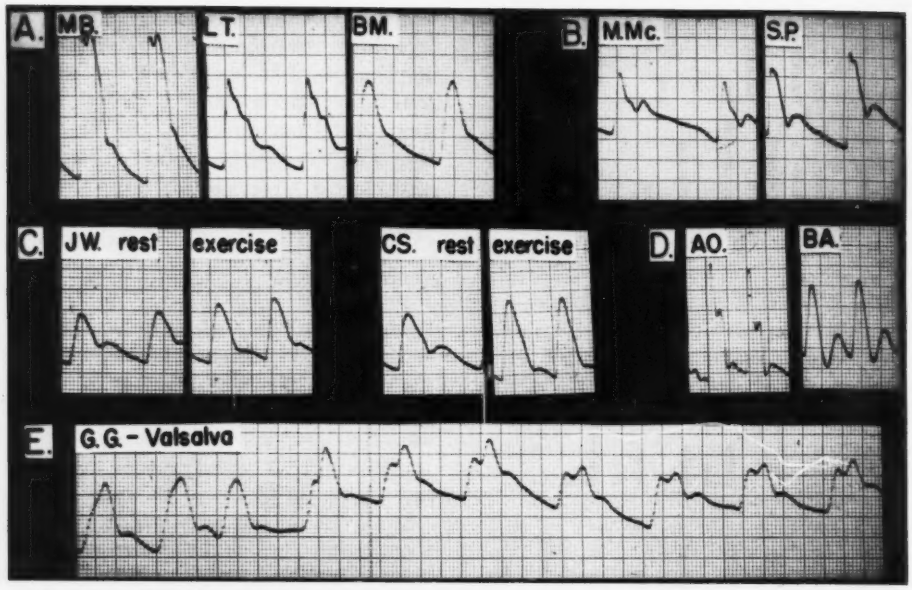

FIG. 4. *A*. Brachial arterial pulse forms from 3 patients (group 5) with severe pure aortic insufficiency. *B*. Brachial arterial pulse forms from 2 patients (group 6) with severe mitral insufficiency, showing the "small collapsing pulse." *C*. Rest and exercise arterial pulse forms in 2 normal subjects. J. W. at rest 114/68, mean 84 mm. Hg, cardiac output 7.7 L./min., stroke volume 103 ml., and peripheral resistance 870 dynes-sec-cm.$^{-5}$; during exercise, arterial pressure 134/72, mean 92 mm. Hg, cardiac output 10.4 L./min., stroke volume 101 ml. and peripheral resistance, 710 dynes-sec-cm.$^{-5}$ There is relatively little change in the pulse contour. C.S. at rest 116/66, mean 76 mm. Hg, cardiac output 6.5 L./min., stroke volume 87 ml., peripheral resistance 930 dynes-sec-cm.$^{-5}$, and exercise arterial pressure 130/72, mean 100 mm. Hg, cardiac output 10.4 L./min., stroke volume 122 ml., peripheral resistance 645 dynes-sec-cm.$^{-5}$ There is a characteristic change in the pulse contour. *D*. The arterial pulse form in other hemodynamic abnormalities. A. O. is a 47-year-old man with hyperthyroidism and atrial fibrillation, arterial pressure 205/75, rate 128, upstroke 0.05 second. B. A. is a patient with fever, anemia, and severe liver disease, arterial pressure 92/50, rate 130, cardiac index 4.4 L./min./M.^{2}, stroke volume 64 ml. The alteration of the pulse contour is apparently related to peripheral vasodilatation without a striking increase in cardiac output.

105 diastolic, and 135 mean. The upstroke duration in group 4 ranged from 0.04 to 0.24 second, mean 0.11 second. This mean value is 0.02 second shorter than the mean of the older group of normal subjects, but because of the wide variability of the myocardial failure group, this difference does not quite reach the 5 per cent level of significance. Uncontrolled factors related to age, hypertension, functional mitral insufficiency, and arterial disease may be involved in this difference and may also be involved in the wide variability within the myocardial failure group. These data, therefore, do not show a significantly shorter upstroke duration in "myocardial failure" as herein defined, than in normal subjects. Because of the finding of a very brief upstroke duration in several patients with severe left ventricular failure, pulsus alternans, and gallop rhythm, however, it is suspected that further studies of larger and better controlled groups might reveal a significant difference.

Aortic Insufficiency (group 5, fig. 4A).

The pulse contours of the patients of group 5 showed some uniformity in the occurrence of abrupt upstrokes, bifid systolic peaks, and small or absent dicrotic waves, but none of these characteristics was constant, and all have been seen in tracings from patients without aortic insufficiency. The procedure was useful as an accurate measurement of the diastolic

pressure, which was not lower than 30 mm. Hg in any of these patients, although sounds were heard down to zero during sphygmomanometric determination of the blood pressure.

Mitral Stenosis and Insufficiency

Mitral stenosis has been associated with no particular features of the arterial pulse contour distinguishable from the normal, though a small pulse pressure with a flattened systolic peak is commonly seen.

Some patients with marked mitral insufficiency have shown the "small collapsing pulse" described by others.[12] Group 6 (fig. 4*B*) includes selected patients showing some degree of this characteristic of the pulse. Their arterial pulse forms show rapid upstrokes, rapid downstrokes, short "systoles," low dicrotic pressures, and prominent dicrotic waves.

Exercise

During exercise, there was a distinct tendency for the systolic and mean pressures to rise somewhat, and for the dicrotic wave to become lower and flatter (fig. 4*C*). The systolic upstroke duration changed very little unless it was prolonged initially, in which case it sometimes became much shorter. Flat-topped curves with apparently long upstrokes were sometimes revealed as quite normal during exercise. These changes were not constant and did not appear to be correlated with the degree of change in cardiac output or peripheral resistance. Many patients showed identical pulse forms during rest and exercise in spite of marked increases in cardiac output. Several patients with elevated cardiac output in association with hyperthyroidism, anemia, or liver disease (fig. 4*D*) showed pulse forms at rest similar to those of other patients during exercise and similar to those of patients with aortic insufficiency.

Discussion

The brachial arterial pressure pulse form is best considered as representing the central aortic pressure pulse, altered in form in the course of transmission to the periphery.[13, 14] This alteration may take place by way of summation of one or more standing waves with the transmitted central aortic pulse. Thus, any changes observed in the brachial arterial pressure pulse may be the result of changes in the central pressure pulse, or of changes in the transmission of the central pulse to the periphery, or both.

The central aortic pressure pulse is a function of the rate and pattern of ventricular ejection, the stroke volume, the distensibility of the aortic chamber, the peripheral vascular resistance, and the viscosity of the blood.[13] The pulse form may be modified by physiologic or pathologic changes in any of these parameters.

Certain pathologic lesions not only affect the central pressure pulse, but also the mode of transmission of the central pulse to the periphery. Dow's experiments[11] showed that the central aortic pulse in aortic stenosis is transmitted to the periphery more faithfully than the normal central pulse. Alexander[15] has found evidence that the aortic standing wave may be reduced by aortic insufficiency, and Gupta and Wiggers[16] have published similar findings in experimental coarctation of the aorta. Recent studies[17] of central and peripheral pulses in man have suggested that the pulse in aortic stenosis is more faithfully transmitted to the periphery. This was also found in a patient with coarctation of the aorta.[18] However, comparisons of the central and peripheral pulse contours in man[19, 20] have so far been few in number.

In view of the multiplicity of central and peripheral factors involved in the genesis of the peripheral pressure pulse, it is not surprising that the brachial arterial tracings encountered in normal subjects vary considerably and overlap to some extent the tracings associated with disorders of the circulation. Nor is the lack of correlation between the duration of upstroke or position of the anacrotic notch with the severity of aortic stenosis in individual patients difficult to accept. On the other hand, the findings presented here do not preclude the possibility that the central aortic pressure pulse may more closely reflect such hemodynamic lesions as aortic stenosis.

Summary

Direct brachial arterial pressure tracings from 250 patients have been analyzed in relation to their potential clinical value.

In 40 "normal subjects" the duration of the

systolic upstroke ranged from 0.06 to 0.20 second, mean 0.11 ± 0.04 second, and the contour of the pulse form showed greater variation than heretofore reported for the human adult. Notching was present on the anacrotic limb in 2 cases. There was a significant increase in the upstroke duration with age.

In 19 of 20 patients with proved severe aortic stenosis characteristic abnormalities of the pressure pulse were evident. The duration of the systolic upstroke was prolonged to a mean of 0.20 ± 0.03 second in this group, and an anacrotic notch was present in 15 cases. While the mean duration of the systolic upstroke was significantly longer than in the normal group, there was some overlap.

The arterial pressure pulses of 13 patients with clinical aortic stenosis proved to be physiologically mild or insignificant resembled those of patients with proved severe stenosis, although the mean upstroke of the group was significantly shorter in duration.

Six patients with proved severe pure aortic insufficiency tended to show characteristic pressure pulses with rapid upstrokes, bifid systolic peaks, and low or flat dicrotic waves. None of these features may be considered diagnostic, since they are also seen in hyperthyroidism, anemia, and other high-output states.

Pulse pressure tracings from a group of 20 patients with decompensated nonvalvular heart disease showed wide variation and did not differ significantly from those obtained from normal subjects, but there was some evidence that both the systolic upstroke and "systole" may be shortened in myocardial failure.

Pulse contours in marked mitral insufficiency may be of the "small collapsing" type.

It is concluded that, because of the many factors that affect the peripheral pressure pulse, such tracings are difficult to interpret as a clinical diagnostic test. They are of value in determining blood pressure accurately. The brachial arterial pulse contour may serve to confirm a clinical diagnosis of aortic stenosis, but is not diagnostic of aortic stenosis and in any individual patient yields no information as to the severity of the lesion. A normal brachial arterial pulse form in a patient suspected of aortic stenosis speaks against physiologically significant stenosis, but does not rule it out. Further studies of the central aortic pulse form and its alteration in transmission to the periphery are indicated, in order to define further the clinical usefulness of arterial pressure tracings.

SUMMARIO IN INTERLINGUA

Registrationes directe del pression arterial brachial ab 250 patientes esseva analysate ab le puncto de vista de lor valor potential pro objectivos clinic.

In 40 subjectos "normal," le duration del ascendita systolic variava ab 0,06 a 0,20 secundas (valor medie = 0,11 ± 0,04 secundas), e le contorno del forma del pulso monstrava plus grande variationes que lo que ha previemente essite reportate pro le adulto human. Indentation esseva presente in le membro anacrotic in 2 casos. Esseva constatate un augmento significative del duration del ascendita con le augmento del etate del subjectos.

In 19 inter 20 patientes con demonstrate sever stenosis aortic, anormalitates characteristic del pulso de pression esseva evidente. Le duration del ascendita systolic esseva prolongate a un valor medie de 0,20 ± 0,03 secundas in iste gruppo, e un indentation anacrotic esseva presente in 15 casos. Durante que le valor medie del duration del ascendita systolic esseva significativemente plus longe que in le gruppo de subjectos normal, le valores del duo series monstrava un certe region de coincidentia.

Le pulsos de pression arterial in le 13 patientes in qui physiologicamente leve o insignificative grados clinic de stenosis aortic esseva demonstrate resimilava illos de patientes con demonstrate sever stenosis, ben que le ascendita medie del gruppo esseva significativemente plus curte.

Sex patientes con demonstrate sever insufficientia aortic pur tendeva a exhibir characteristic pulsos de pression con ascenditas rapide, bifide culmines systolic, e pauco elevate o plan undas dicrotic. Nulle de iste aspectos pote esser considerate como diagnostic, proque illos omnes occurre etiam in hyperthyroidismo, anemia, e altere conditiones de rendimento elevate.

Registrationes del pression pulsatile ab un gruppo de 20 patientes con discompensate morbo cardiac non-valvular exhibiva pronunciate variationes e non differeva significativemente ab le registrationes obtenite ab subjectos normal, sed il pareva haber certe indicationes que tanto le ascendita systolic como etiam le systole pote esser accurtate in disfallimento myocardial.

Contornos del pulso in casos de marcate insufficientia mitral pote esser del "parve typo collabente."

Il es concludite que a causa del numerose factores afficiente le pulso de pression peripheric, tal registrationes es difficile a interpretar como test diagnostic clinic. Illos es de valor in le determination precise del pression de sanguine. Le contorno del pulso arterial brachial pote servir a confirmar un diagnose clinic de stenosis aortic, sed illo non es diagnostic pro stenosis aortic, e in le patiente individual illo non forni informationes in re le severitate del lesion. Un forma normal del pulso arterial brachial in un patiente suspecte de haber stenosis aortic argue contra sed non exclude le possibilitate de un physiologicamente significative stenosis. Studios additional del forma del pulso aortic central e de su alteration in le transmission al peripheria es indicate pro definir plus clarmente le utilitate clinic de registrationes de pression arterial.

Acknowledgment

The authors are grateful for the assistance of Drs. M. A. Gravallese, J. M. Hutcheson, H. J. Kowalski, W. F. McNeely, and R. P. Walker, who obtained many of the arterial pressure records.

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The Normal QRS Loop Observed Three Dimensionally Obtained with the Frank Precordial System

By GEORGE E. SEIDEN, M.D.

By means of a relatively orthogonal lead system combined with the use of an electronic resolver, 3-dimensional QRS loops of normal individuals have been seen broadside in 2 dimensions after proper rotation. QRS loops so visualized have been studied by certain quantitative measurements which it is hoped may be of assistance in distinguishing normal from abnormal loops.

BY MAKING use of a lead system capable of processing body surface potentials to yield reasonably orthogonal QRS dipole components,[1] combined with use of an electronic resolver,[2, 3] capable of rotating the QRS vector loop into 2 dimensions so as to visualize its broadside view, it has been possible to accumulate hitherto unreported data concerning the QRS complex. In this study of normal individuals, it was found that virtually all subjects had relatively simple, open planar loops. The loops exhibited no crossovers, and were invariably transcribed counterclockwise when seen from a direction normal to their respective planes, from above and the left.

METHOD AND MATERIAL

Two hundred seventeen normal male and female individuals were studied. Their age distribution is indicated in table 1. The subjects were largely recruited from faculty and students of the various schools of the University of Pennsylvania. Each subject was examined concerning history of heart disease, pathologic murmurs, hypertension, or failure to pass school, life insurance, or military physical examinations. A positive history of any of these disqualified the subject. Blood pressure measurement of less than 150/100 was obtained from each individual accepted for study. In most instances chest x-rays had been made recently, and any observed cardiac abnormality was cause for disqualification. In those patients referred from the Diagnostic Clinic (which was the source of most subjects over 40 years of age), a complete health history, physical examination, chest x-ray, blood count, urinalysis, and postprandial blood sugar values were demonstrated to be within normal limits. All individuals received standard electrocardiograms, but interpretations were not used to screen subjects, except to eliminate those individuals with arrhythmias other than occasional premature contractions.

The selected subjects were placed in the sitting position and the Frank precordial system of electrode placement was used. The 5 chest electrodes were placed at the level of the fifth rib in the midclavicular line. Cathode followers obviated skin rubbing. Electrode potentials were processed by a resistive adding circuit to yield relatively orthogonal QRS dipole components that were fed into the 3 inputs of an electronic resolver, which presented an oscilloscope view of a projection of the QRS loop whose x'' and y'' components satisfied the equations:

$$P_{x''} = P_x \cos \Phi + P_z \sin \Phi$$
$$P_{y''} = P_y \cos \Theta + (P_z \cos \Phi - P_x \cos \Phi) \sin \Theta$$

where P_x, P_y, P_z represented the unresolved QRS components, Φ the azimuthal angle of rotation around the y axis, and Θ the elevational angle of rotation around the x'' axis. Angle Φ was defined as positive when rotation of the loop around the y axis was clockwise as seen from a direction looking from positive to negative down the y axis. Θ was defined as positive when rotation around the x'' axis was counterclockwise as seen looking down the x'' axis from positive to negative.

The procedure to produce a broadside view of the loop for each individual was as follows. With Φ and Θ of the resolver set to zero, the frontal projection of the QRS loop was pictured on the oscilloscope screen. Angle Φ was then varied by the smallest number of degrees regardless of sign, to produce an edgewise view of the loop (fig. 1*a*). By additional rotation of 90° in the positive direction, the most open loop obtainable by azimuthal rotation about the y axis was pictured, and the final angle Φ necessary to produce this view was recorded. With Φ set at this reading, the loop was rotated in the elevational direction around the newly established x'' axis, through the smallest number of degrees regardless of sign to produce again an edgewise view of the loop (fig. 1*b*). With added positive rotation of

From the Edward B. Robinette Foundation, and the Medical and Diagnostic Clinics, Hospital of the University of Pennsylvania. Sponsored by U.S. Public Health Service grant H-339.

The substance of this paper was presented at the Annual American Heart Association Meetings in Cincinnati, Ohio, October, 1956.

TABLE 1.—*Quantitative Data on the QRS Loop from 217 Normal Subjects*

Number of cases	Age	Average ⏀	Average ⊖	Planarity	Openness
31	50+	75	52	0.11	0.5
35	40–50	88	50	0.11	0.6
45	30–40	80	50	0.11	0.6
106	15–30	78	43	0.13	0.6

90°, the loop was then seen broadside from a direction normal to its plane (fig. 1*c*). The final angle ⊖ required for this view was recorded.

The broadside view of the loop and its 2 edgewise views were photographed by a polaroid land camera. The net result for each subject was a broadside view of his loop, 2 edgewise views, and the angles of rotation ⏀ and ⊖ required to visualize the broadside loop.

Measurements of the loops were made as follows: Planarity in each case was expressed as the ratio of the edgewise width to the longest distance measured across the broadside view. Edgewise width was defined as the shortest distance between 2 parallel lines enclosing the narrowest view of the loop obtainable by either azimuthal or elevational rotation. Openness of the broadside view of the loop was expressed as the ratio of the width of the loop to its length, where length was the longest distance measured across the broadside view and width was the greatest distance across the loop perpendicular to length. In rare instances when the longest distance across the broadside view of the loop could be depicted by lines of equal length but different direction, the direction to define length was chosen whose perpendicular produced the greatest magnitude of width.

RESULTS

Stated qualitatively, the loops were predominantly planar and, when seen broadside from above and the left, transcribed counterclockwise, were relatively simple and open. The average planarity ratio was 0.12 with standard deviation of 0.05. Average ⏀ was 80° with standard deviation of 34°; average ⊖ was 47° with standard deviation of 13°. Openness of loops averaged 0.6 with standard deviation of 0.2. Results according to age groups are shown in table 1. No markedly significant differences due to age were observed, although spread of data in the older age groups was greater as expressed by a greater standard deviation.

In one of the 217 subjects, a 22-year-old normal man, the broadside view of the loop exhibited a single crossover. Loops were otherwise open. All loops were transcribed counterclockwise as seen from above and the left. In 2 instances, the degree of nonplanarity was sufficiently great so as to render useless the rotational procedure. Both of these individuals, aged 51 and 46 respectively, appeared to be normal after complete studies in the Diagnostic Clinic. Standard electrocardiographic readings were "possible conduction defect" and "probable left ventricular hypertrophy" respectively.

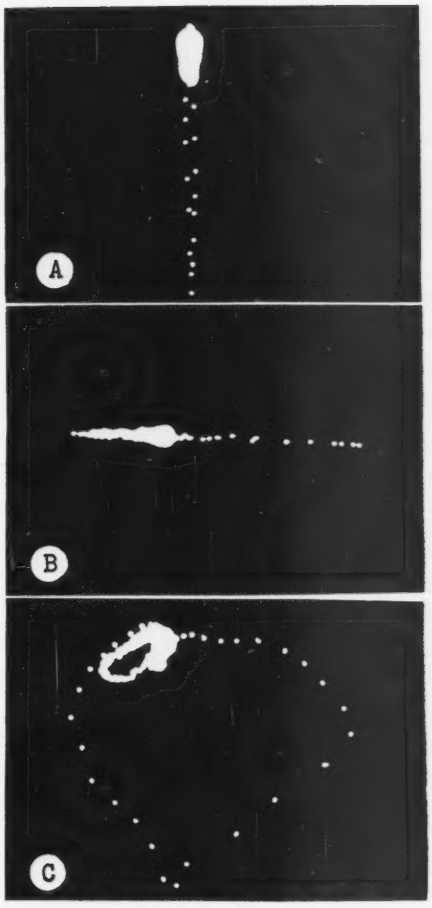

FIG. 1. *A*. Photograph of edgewise view of the loop of a subject. This view was obtained by ⏀ rotation (azimuthal). *B*. Photograph of edgewise view obtained by ⊖ rotation (elevational). *C* Broadside view of subject's loop.

In the great majority of cases, the standard electrocardiograms of subjects were reported as normal. Occasional readings of right bundle-branch conduction defect were reported, but in these cases the loops were often within the standard deviations of the various measurements. There were no instances of standard electrocardiographic readings of typical right or left bundle-branch block.

Discussion

The Frank precordial system has been shown to yield orthogonal components with accuracy of image vectors within ±5 per cent in angle and ±20 per cent in length, for dipole locations within a prescribed 5 cm. by 5 cm. square area at dipole level in a human-shaped model. The assumption that nearly all the subjects in this series had dipole locations in the 5 cm. by 5 cm. square area is probably valid, in that a study of dipole locations in patients with various kinds of severe heart disease and abnormally shaped hearts revealed locations in 36 of 40 cases to be in this area.[4] Studies of normal subjects indicated an even tighter cluster of dipole locations.[5]

However, as employed in this study, the Frank precordial system suffers from error in rendering orthogonal components due to location of the belt of chest electrodes at the level of the fifth rib. Undoubtedly this was not the exact dipole level in many instances. The level of the fifth rib was selected after a study of 100 normal chest x-rays of individuals of varying age and sex revealed that in 81 cases the level of the anatomic center of the heart was between the fourth and fifth interspaces in the midclavicular line. It was considered that the technical simplicity of using the fifth rib level in all cases outweighed the ensuing loss of accuracy, which, to be overcome would require the use of more body surface electrodes. In a limited study of 5 individuals, varying the belt level upward or downward for a distance of 1 inch altered the data, but within the limits of the standard deviations of the various measurements. Although the broadside view of the loop was slightly modified by changes in belt height, its shape remained relatively simple and open.

The significance of the results of this study of 217 normal persons is the relative similarity of loops when seen in broadside view, divorced from an anatomic frame of reference, as rendered by a reasonably orthogonal lead system. It should be pointed out that if the dipole hypothesis is valid with small percentage error for normal subjects and patients with heart disease as previous studies have suggested,[6-8] and when loops are predominantly planar as is the case in most normal persons, then the broadside view of the loop and the rotational angles $\oplus$ and $\ominus$ required to visualize it represent all of the QRS information obtainable by standard 12-lead electrocardiography, plus the additional information of the time relationships between the leads. Considered in this light, visualization of the broadside loop derived from an orthogonal lead system represents a simplification of electrocardiographic methods, and yet at the same time enables us to make meaningful quantitative studies of the QRS complex not hitherto possible. It is hoped that such studies will lead to more accurate separation of normal from abnormal subjects.

It is of theoretical significance that the results of this study confirm Milnor's[9] and Frank's[10] observations of the planarity of loops, and call for an explanation of this phenomenon in terms of spread of depolarization in the heart. Furthermore, as pointed out by Frank,[10] the planarity of loops may explain the finding of constant QRS wave form loci on the body surface, described originally by Wolferth, Livezey, and Wood.[11]

Summary

By means of a relatively orthogonal lead system combined with the use of an electronic resolver, 3 dimensional QRS loops of normal individuals have been seen broadside in 2 dimensions after proper rotation. QRS loops so visualized have been found to be relatively simple, open, planar, without crossovers, and to be transcribed counterclockwise as viewed from above and the left. Certain quantitative measurements of these loops have been made, which it is hoped will in the future help to distinguish normal from abnormal individuals.

Acknowledgment

The author expresses appreciation for the technical assistance of Miss Deborah Packman, and to Dr. Calvin F. Kay for helpful suggestions.

Summario in Interlingua

Per medio de un relativemente orthogonal systema de derivation, combinate con le uso de un resolutor electronic, spiras QRS tridimensional ab individuos normal esseva visualisate bidimensionalmente post appropriate grados de rotation. Spiras QRS assi visualisate se ha provate relativemente simple, aperte, planar, libere de transcruciamento, e transcripte in direction sinistrorse in lor aspecto ab in alto e al sinistra. Certe mesurationes quantitative de tal spiras ha essite executate. Il es a sperar que illos va esser de adjuta in distinguer individuos normal ab individuos anormal.

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In the summer of the year 1776, I ordered a quantity of the leaves to be dried, and as it then became possible to ascertain its doses, it was gradually adopted by the medical practitioners in the circle of my acquaintance.—William Withering. *An Account of the Foxglove, and Some of Its Medical Uses.* Birmingham, 1785.

Truncus Arteriosus

Clinical Study of Fourteen Cases

By Ray C. Anderson, Ph.D., M.D., William Obata, M.D., and C. Walton Lillehei, M.D., Ph.D.

We have encountered difficulty in recognizing and identifying clinically true truncus arteriosus with pulmonary arteries (type 1) because of its resemblance to correctable cardiac defects such as patent ductus arteriosus, aortic-pulmonic defect, and ventricular septal defect. In the present report we are presenting clinical information on 14 patients with this anomaly, both to supplement the scanty data available in the literature and to emphasize the need for correct diagnosis.

PERSISTENT truncus arteriosus is defined as a single trunk arising from the heart and supplying the coronary, pulmonary, and systemic circulations, with no remnants of an atretic aorta or pulmonary artery.[1-3] The number of semilunar cusps may vary from 2 to 6. Typically a defect is present in the bulbar portion of the anterior ventricular septum, a defect lying just under the semilunar cusps and entirely different from the usual ventricular septal defect involving or bordering on the membranous portion of the septum. Photographs of an autopsy specimen (case 10) are shown in figures 1 and 2.

Considerable disagreement has arisen in the classification of truncus defects, particularly with regard to the inclusion of cases having only bronchial circulation to the lungs. Moragues[4] preferred to exclude such cases, whereas Collet and Edwards[3] included them as a special subtype. Kjellberg and associates[5] included them with the "pseudotruncus" group because of the great clinical similarity. Manhoff and Howe[6] included truncus arteriosus in their classification of defects involving absent or anomalous pulmonary arteries. MacGilpin[7] separated cases with 1 pulmonary artery from those with 2. Cases have also been classified as to the origin of the trunk, whether from the right ventricle or left ventricle or "overriding," or whether a single ventricle is present.[8]

The following simplified classification is modified from those of previous workers. This classification not only follows natural embryologic and anatomic divisions, but also appears to be practical from a clinical viewpoint. Whether the pulmonary arteries arise separately but in very close approximation, or whether the pulmonary artery arises singly and then divides into 2 main branches, is often difficult to decide in individual cases, even at the autopsy table. Since such cases are closely related embryologically and clinically, it appeared logical to combine those cases previously called type 1, type 2, and type 3 by Collett and Edwards.[3] On the other hand, the absence of 1 pulmonary artery changes the clinical picture considerably, and to us merits separate classification.

In view of the considerable differences of opinion regarding classification, it seems advisable for individual cases to be referred to in descriptive terms (true truncus arteriosus with pulmonary arteries, true truncus arteriosus with absent pulmonary arteries, etc.) rather than in arbitrary terms (type 1, type 2, etc.). Unfortunately, there are some intermediate cases, with relatively small pulmonary arteries and large bronchial arteries (case 6 in present series). Likewise, as will be discussed later, cases of our type 1 truncus arteriosus do not approach a stereotyped clinical pattern, and associated defects may modify the picture even further.

Classification of Truncus Malformations

True Truncus Arteriosus

Type 1. True truncus arteriosus, with pulmonary arteries arising from the trunk proximal

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This work was aided by a grant from the Minnesota Heart Association.

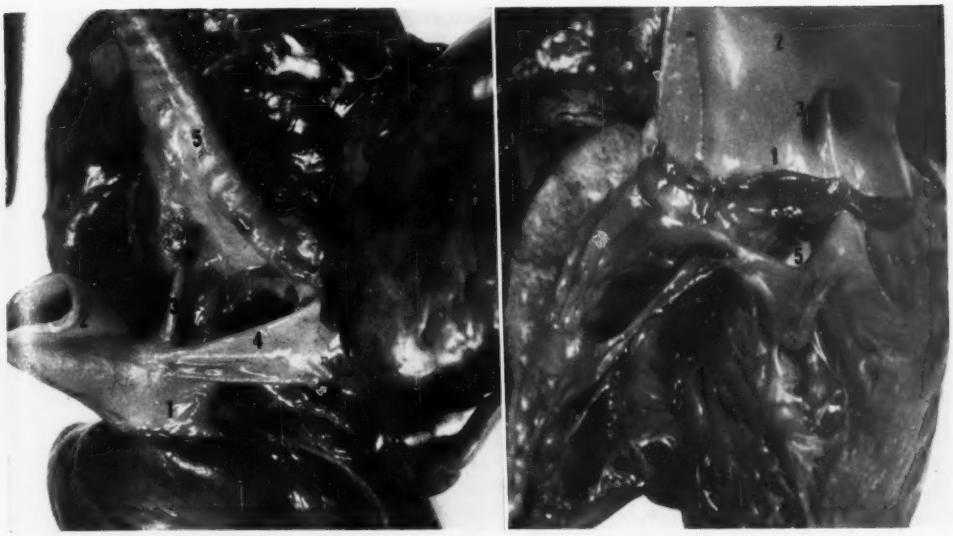

FIG. 1 *Left.* Photograph of heart in case 10. Left superior view. Note side-by-side origin of pulmonary arteries. 1, truncus arteriosus; 2, aorta; 3, right pulmonary artery; 4, left pulmonary artery; and 5, trachea.

FIG. 2 *Right.* Photograph of heart in case 10. Trunk and right ventricle opened anteriorly. 1, truncus arteriosus; 2; aorta; 3, right pulmonary artery; 4, left pulmonary artery; and 5, ventricular septal defect.

to the innominate artery (includes types 1–3 of Collett and Edwards[3]).

Type 2. True truncus arteriosus, with absence of 1 pulmonary artery.

Type 3. True truncus arteriosus, with absence of both pulmonary arteries.

Type 4. Partial truncus arteriosus (aortic-pulmonic defect or "window").

"*Pseudotruncus*"

Type 1. Solitary aortic trunk with pulmonary atresia.

Type 2. Solitary pulmonic trunk with aortic atresia.

The embryologic features of persistent truncus arteriosus, as well as the case literature, have been carefully reviewed by Humphreys,[9] Lev and Saphir,[2] Collett and Edwards,[3] and MacGilpin.[7] On the other hand, relatively little has been written regarding the clinical picture presented by patients with this defect. We have studied 14 cases of true truncus arteriosus having 2 pulmonary arteries (type 1) and have been impressed by the wide range and confusing nature of the clinical findings. These 14 cases have all been verified by surgical exploration or postmortem examination. We have studied an additional half dozen cases in which persistent truncus arteriosus of similar type has been diagnosed clinically, but which are being omitted in view of the lack of direct confirmation.

The clinical and laboratory data on these 14 cases are summarized in tables 1 to 5. In addition, 1 case is being reported in detail to illustrate the difficulties in clinical diagnosis.

CASE REPORT

Case 3 (R.O.). This boy was referred to University Hospitals on August 31, 1950, at the age of 4 years. The mother reported that she had had a 2-day attack of mild measles (rubella?) during the first trimester of pregnancy, and that a daughter had had a similar illness at the same time. A heart murmur had been first heard when the boy was 2 months of age. During his first year of life he gained poorly and suffered 2 attacks of pneumonia. Subsequently he did well, except for slight dyspnea on exertion.

On examination, the boy appeared small for his age, weighing only 31 pounds and measuring 38 inches in height. No cyanosis was noted. A precordial bulge was present. There was a soft systolic thrill and short harsh systolic murmur along the lower left sternal border. The pulmonic second sound was not

TABLE 1.—*Clinical Data*

Case	Birth date	Sex	Diagnosis established		Onset of cyanosis	Precordial bulge	Blood pressure	Thrills	Murmurs		
			Method	Age					Type	Grade	Location
1. C. P.	1930	F	Autopsy	16 years	2 years	—	124/88	S	S	Loud	LSB
									D	—	ULSB
2. D. P.	1950	M	Autopsy	4 months	6 weeks	—	—	none	S	3	LLSB
3. R. O.	1946	M	Surgery	8 years	none	+	84/50	S	S	3	LSB
									D	1	ULSB
4. L. K.	1952	F	Autopsy	2 months	birth	+	102/68	S	S	Loud	Base
5. V. E.	1953	F	Surgery	2 years	1 year	+	98/60	S	S	4	LSB
6. M. H.	1953	F	Autopsy	5 months	birth	—	90/60	none	S	3	LSB
7. D. R.	1953	M	Autopsy	3 months	none	—	88/–	S	S	4	LSB
8. M. M.	1954	M	Autopsy	10 days	birth	—	—	none	S	2	LSB
9. H. W.	1948	M	Autopsy	7 years	none	+	110/40	S	S	4	LLSB
									D	1	ULSB
10. J. G.	1956	M	Autopsy	1 month	8 days	+	60/–	none	S	3	LLSB
11. P. W.	1956	M	Autopsy	2 months	6 weeks	+	100/–	S	S	4	LSB
12. T. W.	1956	M	Autopsy	5 months	2 weeks	+	80/30	none	S	4	LSB
13. D. L.	1956	M	Autopsy	2 months	birth	—	70/–	none	S	3	RSB
14. C. T.	1953	M	Surgery	3 years	since infancy on crying only	+	100/70	S	S	3	Apex

S, systolic; D, diastolic; ULSB, upper left sternal border; LLSB, lower left sternal border; LSB, left sternal border; and RSB, right sternal border.

TABLE 2.—*Electrocardiographic Data and Hemoglobin Levels*

Case	Age	Hemoglobin	Axis	P wave voltage lead II (mv.)	PR interval	Rate	S/R V_6	R/S V^6	Miscellaneous
1. C. P.	16 y	19.3	+150	0.50	0.20	90	—	—	On digitalis
2. D. P.	4 m	14.4	+80	0.20	0.10	140	—	—	—
3. R. O.	8 y	15.0	+110	0.24	0.17	90	14/2	16/35	Notched P_1
4. L. K.	2 m	17.1	+95	0.35	0.12	150	27/36	17/2	+T in V_1
5. V. E.	2 y	16.4	+140	0.32	0.12	140	30/26	22/13	—
6. M. H.	5 m	16.8	+85	0.23	0.12	160	8/8	30/0	—
7. D. R.	3 m	12.2	+95	0.30	0.12	170	14/1	25/5	—
8. M. M.	10 d	—	—	—	—	—	—	—	—
9. H. W.	7 y	15.0	+65	0.27	0.14	110	20/22	30/0	Notched P_1. Negative T in leads I, V_5, V_6
10. J. G.	1 m	16.7	+105	0.28	0.13	140	14/0	12/7	—
11. P. W.	2 m	14.2	+80	0.30	0.12	150	18/17	24/0	Negative T in V_6. On digitalis
12. T. W.	5 m	13.2	−30	0.40	0.10	140	25/2	45/20	—
13. D. L.	2 m	14.3	+95	0.12	0.10	140	Dextrocardia V2-4/10	RV6-24/2	—
14. C. T.	3 y	12.8	+85	0.25	0.12	140	16/5	6/8	—

accentuated and was followed by a long blowing diastolic murmur. Blood pressure was 90/60 in the right arm. The hemoglobin concentration was 12.5 Gm./100 ml. and the hematocrit value was 37 per cent. The electrocardiogram (no precordial leads) showed an axis of +100 degrees and notching of the P waves in lead I. Roentgenography showed moderate cardiac enlargement, involving both ventricles, with increased pulmonary vascular markings.

A diagnosis of interatrial septal defect was considered most likely. Cardiac catheterization was then performed, and an increase in oxygen content was found in the "main pulmonary artery" as compared to the right ventricle. Angiocardiography at this

TABLE 3.—*Roentgenographic Findings*

Case	Heart size	Chamber enlargement			Upper left border	Pulmonary vascular markings	Aortic arch	Miscellaneous	Angiocardiogram
		RV	LV	LA					
1. C. P.	4+	4+	4+	N	Marked bulge	3+	L-large	Emphysema	—
2. D. P.	2+	2+	2+	1+	Convexity	2+	L	—	—
3. R. O.	2+	2+	2+	N	Convexity	3+	R-large	—	No early filling of aorta
4. L. K.	2+	3+	1+	N	Slight convexity	1+	L-large	Heart shifted to right	Right to left shunt in atrium; simultaneous filling of PA and aorta
5. V. E.	3+	3+	3+	2+	Flat	2+	R	—	Inadequate
6. M. H.	3+	3+	1+	1+	Flat	2+	R	—	RPA filled from trunk, LPA from descending aorta. Aortogram: RPA filled from R ductus, LPA from descending aorta
7. D. R.	3+	2+	4+	2+	Flat	3+	L	—	—
8. M. M.	—	—	—	—	—	—	—	—	—
9. H. W.	3+	2+	2+	2+	Flat	3+	L-large	—	—
10. J. G.	3+	2+	2+	N	—	2+	L	Ledge in LAO	Inadequate
11. P. W.	3+	3+	3+	2+	Slight convexity	3+	L	—	—
12. T. W.	3+	3+	1+	1+	Marked concavity	3+	L	—	Simultaneous filling of PA and aorta
13. D. L.	3+	—	—	—	—	2+	L	Heart in right chest	—
14. C. T.	1+	N	1+	N	Slight convexity	2+	R	—	No early filling of aorta

time showed normal filling of the pulmonary vessels, with a suggestion of minimal opacification of the descending aorta. On the basis of these findings a diagnosis of aortic-pulmonic "window" was considered most likely.

The boy was next seen 2 years later (1953) and was then reported to be getting along well. No cyanosis was noted at that time. A precordial bulge and systolic and diastolic murmurs were again noted. Blood pressure was 84/50 in the right arm. The preferred diagnosis was now Eisenmenger complex, a diagnosis made meanwhile at another cardiac clinic.

In 1954 his case was reviewed and the possibility of a reversing patent ductus arteriosus was considered. Simultaneous blood samples were obtained from the right brachial and femoral arteries, but both showed equal degrees of desaturation. He was readmitted for repeat cardiac catheterization in September 1954. At this time he was still reported to have only mild exertional dyspnea. He appeared small and showed no cyanosis. Cardiac findings were essentially unchanged, except that mention was now made of accentuation of the pulmonic second sound. The hemoglobin concentration was 15.0 Gm./100 ml. and the hematocrit level was 44 per cent. The electrocardiogram showed an axis of +110 degrees notched P waves in lead I, and evidence of right ventricular preponderance on the precordial leads (R/S in V_1 was 14/2; in V_6, 16/35). Roentgenography again showed considerable cardiac enlargement, with marked prominence of the "pulmonary artery segment" and pulmonary vasculature; the aortic arch was on the right (fig. 3). At cardiac catheterization the catheter tip was passed into the ascending and descending aorta, but the pulmonary arteries could not be entered. The findings were considered to indicate a ventricular septal defect with bidirectional shunt.

Cardiac surgery was scheduled for October 8, 1954, with the use of the cross-circulation technic. On opening the pericardium the surgeons identified a truncus arteriosus defect. The main vessel measured 7.5 cm. in diameter. Approximately 3 cm. above the origin of this trunk there arose a pulmonary artery, 3 cm. in diameter, which then divided into left and right branches. No attempt at correction was made. Convalescence was without complications and the patient was discharged on the eleventh postoperative day. He was next seen in April 1955, at which time he was reported to be getting along very

TABLE 4.—*Cardiac Catheterization Data*

Location*	Case 3†		Case 4		Case 9‡		Case 14§	
	1/12/51	9/29/54	1/28/55	2/1/55	8/5/55		8/9/56	9/25/56
Oxygen Content in ml./100 (Saturations in Parentheses)								
SVC	11.1	12.4	6.2	5.9	12.7	—	9.4	9.6
IVC	9.4	11.1	2.6	—	—	—	9.4	—
RA	10.7	11.6	6.4	6.6	11.7	—	10.8	8.4
	12.2		5.0				10.6	
RV	12.4	14.3	4.0	7.0	12.8	12.1	10.5	8.5
	12.9				12.8	12.4	10.6	
"PA"	—	—	—	—	14.5	13.7	—	—
"MPA"	14.4	—	—	8.3	—	—	—	—
"RPA"	14.8	—	—	—	—	—	—	—
Car Art	—	—	—	—	—	12.1	15.7	—
R Br Art	—	16.7 (90%)	—	—	—	—	—	—
L Br Art	—	—	—	9.4	—	—	—	—
Aorta	—	16.5	—	—	—	—	—	12.9
		17.0						12.9
								12.8
								13.7
								14.3
Fem Art	14.9 (88%)	—	8.1 (56%)	7.5 (55%)	15.2 (92%)	12.2 (74%)	15.6 (89%)	—
Pressure in mm. Hg								
RA	0/–8	—	10/2	8/–3	9/–1	—	9/2	—
RV	68/10	110/0	110/0	90/30	95/3	—	95/5	—
"PA"	—	—	—	—	92/60	—	—	—
"MPA"	60/54	—	—	90/62	—	—	—	—
"RPA"	60/40	—	—	—	—	—	—	—
Car Art	—	—	—	—	—	106/91	—	—
L Br Art	—	—	—	100/45	—	—	—	—
Aorta	—	100/60	—	—	—	—	95/51	—
Fem Art	—	—	—	—	99/51	125/68	—	—

* Quotation marks are used to indicate doubt as to correct identification of location, though they were called this at the time of cardiac catheterization.

† Simultaneously drawn samples of blood (8/19/54) from right brachial artery and femoral artery showed equal degrees of oxygen desaturation (88 per cent).

‡ Two sets of data obtained at different times during same cardiac catheterization. Repeat femoral artery oxygen determination on 11/8/55 showed 92.8 per cent saturation.

§ Samples from aorta in second cardiac catheterization were taken as catheter tip was slowly withdrawn from descending aorta (14.3) to "ascending aorta" just above valve (12.9).

well, with little or no cardiac symptoms. His weight was only 49 pounds (age 8 years), and height, 48 inches. The cardiac findings were unchanged.

ADDITIONAL DATA

Various data not included in the tables are also of interest. Among the 13 cases in which detailed pregnancy histories were obtained, there was a history of "mild measles" in one (case 3), inadequate diet in another (case 9), and polyhydramnios in a third (case 6). Birth weights showed a normal average of slightly over 7 pounds, though in 1 case the birth weight was only 4¼ pounds. Twelve of the 14 births occurred between June 15 and December 15. There were 10 males and 4 females. None of the patients was a member of a twin pair. There were 13 older living siblings; of these, 2 had cyanotic congenital heart defects. One

TABLE 5.—*Autopsy and Surgical Findings*

Case	Number of semilunar cusps	Origin of trunk	Origin of pulmonary arteries	Other cardiac defects	Noncardiac defects
1. C. P.	3	—	As one vessel	—	Kyphosis
2. D. P.	3	Both V	As one vessel	Single coronary ostium	—
3. R. O.	—	—	As one vessel*	—	—
4. L. K.	3	Both V	As one vessel	Right pulmonary veins return to right atrium; atrial septal defect; small tricuspid leaflets	Rudimentary thumb. Diaphragmatic hernia. Lung anomalies
5. V. E.	—	—	Side-by-side*	—	—
6. M. H.	3	RV	As one vessel	3 mm. right PDA; large left (4 mm.) and right (2 mm.) bronchial arteries	Microphthalmus
7 D. R.	2	RV	—	—	—
8. M. M.	3	RV	Side-by-side	Interruption of aortic arch; atrial septal defect	—
9. H. W.	3	Both V	Side-by-side	—	—
10. J. G.	3	Both V	Side-by-side	—	Horseshoe kidney
11. P. W.	3	Both V	As one vessel	—	—
12. T. W.	2	Both V	As one vessel	—	Diverticulum of jejunum
13. D. L.	3	Both V	Side-by-side	Nonmirror image dextrocardia. Tricuspid atresia; pulmonary arteries arose from right posterior aspect of trunk; left aortic arch	—
14. C. T.	—	—	As one vessel*	—	—

* Observation made at surgery.

older sibling had died at birth "with the cord around his neck." There were only 2 younger siblings, both apparently normal. Case 6 was of considerable interest, since the mother has had 4 children by 4 different men; the oldest child has cerebral palsy and mental retardation, the next has cyanotic congenital heart disease (probably severe tetralogy of Fallot), the next is case 6, and the fourth, just recently born, is said to be normal. The foregoing data are too limited in themselves to allow for any conclusions, but if combined with data of others, may be of value. Whether the seasonal incidence mentioned above is of etiologic significance, as in patent ductus arteriosus, remains to be seen.

DISCUSSION

General Features

As already mentioned, our 14 cases presented a wide variety of clinical findings. The majority died in early infancy, but 3 lived to at least 7 years of age. Abbott[1] tabulated 21 cases with death occurring from birth to 25 years, the average being 4 years. In his review of the literature MacGilpin[7] cited cases living up to the age of 36 years, but 85 per cent died before 2 years of age. Incidentally, cases of truncus arteriosus without pulmonary arteries showed a slightly better life expectancy in both of these series of cases. In both there was a slight excess of males.

Growth retardation was a typical feature of all of our cases, even in those dying in infancy. Respiratory infections tended to be frequent and severe, though in 2 of our oldest cases this did not represent a problem after the first 2 years of life. Dyspnea developed sooner or later in all, but in our cases did not necessarily parallel the level of cyanosis. The patient may die in either left or right heart failure.

Physical Findings (table 1)

Other writers[10-12] have described cyanosis (some pointing out that it may be minimal or even absent) and a loud parasternal systolic murmur, with occasionally a machinery-type

murmur, as characteristic findings. Contro and associates[13] reported 4 cases mimicking patent ductus arteriosus, in 3 of which there was a rumbling murmur extending through systole into but not through diastole; however, the murmur was not considered to be of typical ductus quality, nor was it the "familiar soft continuous bruit commonly heard in patients with truncus and dilated bronchial arteries." Our cases showed extreme variations in cyanosis, from absent to severe, even in those of equal age. Loud systolic murmurs along the left sternal border were present in all of our cases, usually with an associated thrill; but a diastolic murmur was heard only in the 3 oldest cases, where it was present over the pulmonic area. In none was there a machinery-type murmur. Apparently a true machinery-type murmur is rare or exceptional in type 1 truncus arteriosus defects, and the widespread impression that it does occur has probably arisen from the observations of continuous systolic-diastolic bruits in type 3 truncus arteriosus defects (absent pulmonary arteries, pulmonary circulation being by way of large bronchial arteries).

Taussig[10] described a loud pure second sound over the base as a specific feature of this defect, a sign emphasized also by others.[12, 14] Unfortunately, in our series of cases, with the exception of the 3 most recent cases, examiners failed to comment on the nature of the second sound except to mention its intensity. However, no mention was made in any case of a split second sound over the base. On the other hand, Gøtzsche[15] and Singleton's group[16] have both reported clinically diagnosed cases of truncus arteriosus with split second sounds. Neither of these cases has been verified by direct observation. It is possible that other heart sounds could mimic a splitting, but it is difficult to reconcile a true splitting of the second sound with this defect. Phonocardiography might well prove to be extremely useful in evaluating the nature of the second heart sound when a truncus arteriosus defect is suspected.

Blood pressures showed no consistent pattern as far as pulse pressure was concerned and were generally within normal limits. A precordial bulge appeared to be one of the more characteristic findings.

Electrocardiographic Findings (table 2)

As with other clinical features, the electrocardiogram in our cases showed considerable variation. Uusally there was slight right axis deviation, a finding normal in the age range studied. Peaking of the P waves in lead II appeared to be the only frequent abnormal finding. Of the 2 older children with minimal arterial oxygen desaturation, one had right ventricular preponderance and the other had left ventricular preponderance as well as left ventricular strain. In general there is little of diagnostic significance in the electrocardiogram, a comment already made by Taussig.[10] Others have mentioned right axis deviation[11] or either right, left, or combined ventricular hypertrophy.[13, 14]

Roentgenographic Findings (table 3)

Taussig[17] described the typical roentgenographic findings of truncus arteriosus, including type 1 and type 3, in infancy as cardiac enlargement, pulmonary concavity, upturned apex, a prominent aortic knob, and a "shelf" in the left anterior oblique view. In older patients the heart was said to have a contour similar to a tetralogy of Fallot with severe pulmonary stenosis. If the lungs were supplied only by bronchial arteries (type 3 in our classification), then there was said to be diminished hilar shadows. Gasul and co-workers[12] have also emphasized pulmonary concavity, upturned apex, and prominent aortic knob. Abrams[18] has described a high "hilar comma" and the frequent occurrence of a right aortic arch in this defect.

In our cases roentgenography has typically shown moderate to marked cardiac enlargement, with right as well as some left ventricular enlargement, and a moderate increase in pulmonary vascular markings. The left atrium was enlarged in about half the cases. No typical cardiac contour was found, but an oval or egg-shaped outline, as described by Rowe and Vlad[14] in a case with a right aortic arch, was seen several times. We encountered it however in cases with left aortic arch but in none of the 4 cases with right aortic arch. The "pulmonary artery segment" (upper left border) was generally flat, but in several instances showed a

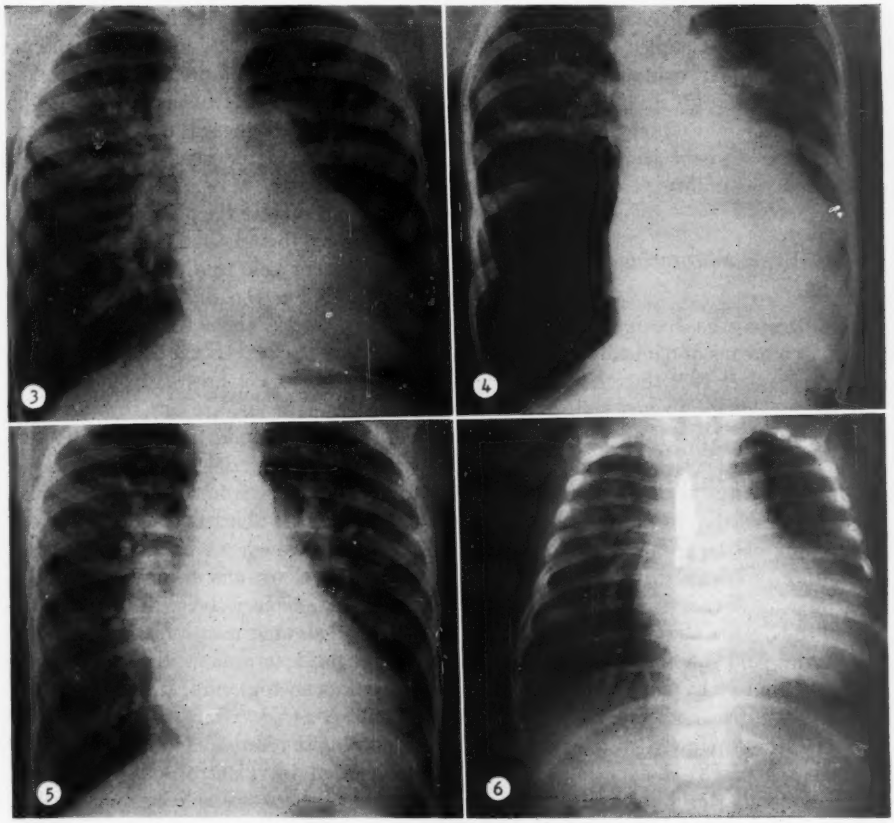

FIG. 3. Roentgenogram of chest in case 3. Posteroanterior view. Age 8 years. Note right aortic arch.
FIG. 4. Roentgenogram of chest in case 1. Posteroanterior view. Age 16 years. Note emphysema.
FIG. 5. Roentgenogram of chest in case 9. Posteroanterior view. Age 7 years.
FIG. 6. Roentgenogram of chest in case 7. Posteroanterior view. Age 3 months.

prominent though rather high bulge that actually represented the left pulmonary artery; this bulge could be identified as being separate from the heart border in this area sometimes on the plain films and sometimes on fluoroscopy. Variations in cardiac contour are illustrated in figures 3 to 6.

In only a minority of cases was the "ascending aorta" or "aortic knob" noted to be very large. A "shelf" in the left oblique view was seen in only 1 case; incidentally, this "shelf" is frequently seen in cases of true truncus arteriosus with absent pulmonary arteries (type 3 in our classification) or in "pseudotruncus." We found a high "hilar comma" to be present in about half of our cases, particularly in the older patients.

Since the main pulmonary artery segment is absent anatomically in true truncus arteriosus, careful film and fluoroscopic observation should be made to determine its absence. In infants, observation is made difficult by the thymus gland, which so often obscures the region of the main pulmonary artery segment. In the presence of increased pulmonary vascular flow, transposition of the great vessels and its subtypes (transposition with tricuspid atresia, corrected transposition, and single ventricle with transposition and rudimentary outflow for the aorta) are the only other conditions that also have absent main pulmonary artery segments on roentgen examination. Therefore, if the absence of the main pulmonary artery segment can be determined, the finding becomes im-

portant in that it immediately excludes a number of conditions. Coupled with the other findings of high "hilar comma," active and often prominent "aorta," and increased pulmonary vascularity, the absence of the main pulmonary artery segment should direct one's attention to the possibility of a true truncus arteriosus defect.

Findings on Angiocardiography and Aortography (table 3)

Angiocardiography has been generally used or described as a means of clinically identifying truncus arteriosus,[5, 14, 18, 19] though apparently no one individual or group has had extensive experience with this type of defect. Nevertheless, Abrams[18] believed it to be the only method of establishing a conclusive diagnosis of truncus arteriosus. He stated that in this defect there is immediate filling of the trunk from the right ventricle, with no contrast material in the pulmonary artery until the trunk is filled; the trunk is said to be twice the ordinary size of an ascending aorta, and becomes much smaller beyond the isthmus; the left ventricle often fills through the ventricular septal defect. None of the above authors referred to failures or to the difficulties that might be expected in cases where the peripheral arterial oxygen saturation approaches normal values. However, DeGroot[20] mentioned 1 failure, and recommended that angiocardiograms be obtained in both the anteroposterior and left oblique positions.

Our experience with angiocardiography in cases of truncus arteriosus is limited. This procedure was done in 7 of the patients here reported. We have not had the benefit of a biplane camera, a very limiting factor in our opinion. In several of our cases, technical difficulties resulted in nondiagnostic films. Angiocardiography permitted a positive diagnosis in cases 6 and 12. Both of these patients were cyanotic, and consequently simultaneous opacification of the trunk, pulmonary arteries, and aorta would be expected. On the other hand, in cases 3 and 14, who were only minimally desaturated, the aorta did not opacify sufficiently for early radiologic detection.

Aortography as a means of diagnosing truncus arteriosus defects has been used very little, or at least little has been published on this subject. In describing their experience with aortography in infants, Keith and Forsyth[21] include 1 case of truncus arteriosus that was erroneously diagnosed by aortography as a patent ductus arteriosus. With reference to such confusion, they write, "It may be difficult at times to eliminate the possibility of a persistent truncus by this method, but there are certain features that help to differentiate the two conditions. When the ductus fills from the pulmonary artery, the latter usually shows as a large vessel close to the aorta. On the other hand, the vessels arising from the aorta, in persistent truncus, are apt to be smaller than the main pulmonary artery. In persistent truncus, one may detect that the vessels going to the lung arise from the ascending aorta and in this way be able to distinguish them from the ductus which arises from the descending aorta." Singleton and associates[16] found aortography of ancillary help in 1 of their cases. Abrams[22] also has mentioned possible confusion of truncus arteriosus with patent ductus arteriosus on aortography, but apparently did not consider this procedure particularly useful in diagnosing the former. This confusion is further emphasized by Contro and associates,[13] who reported 4 cases of clinically diagnosed "atypical" patent ductus arteriosus, with retrograde arteriograms showing opacification of the pulmonary vessels from the aorta, but which at surgery proved to be truncus arteriosus defects.

Only 1 of our cases had aortography, and in this instance (case 6) it was of some diagnostic help. If aortography is to be performed, it would appear ideal to do the injection through a catheter, with the tip of the catheter in the "ascending arch." One would expect the force of injection to alter locally the hemodynamics of blood flow, and thereby disrupt the "streaming" patterns in the single trunk and allow for simultaneous opacification of the pulmonary arteries and aorta. This would be particularly useful in those cases where the systemic arterial oxygen saturation approaches normal. To be sure, there would be some confusion with a partial truncus (aortic-pulmonic defect), and other diagnostic information would be necessary.

TABLE 6.—*Differential Diagnosis for a Patient with Cardiomegaly, Increased Pulmonary Vasculature, Pulmonary Hypertension, and Borderline to Slightly Decreased Systemic Arterial Oxygen Saturation*

Defect	Second heart sound	Size of "ascending aorta"	Cardiac catheter passes into		Increase in oxygen content occurs in
			"Ascending aorta" and carotid artery	Pulmonary artery branches	
Truncus arteriosus	Always pure	Large	Usually	Seldom	"PA" or Truncus and also usually RV
Patent ductus arteriosus	Usually split	Large	Never	Almost always	PA if nonreversing
Aortic-pulmonic defect	Usually split	Normal to large	Often	Almost always	PA
Ventricular septal defect	Usually split	Small	Occasionally	Almost always	RV

Cardiac Catheterization Findings (table 4)

Our limited experience with cardiac catheterization in this defect does not allow for broad generalizations. Actually, we were misled several times by misinterpretation of the data presented in table 4. It is obvious that pressures in the right ventricle will approximate those in the left. Likewise, because of the ventricular septal defect, the oxygen content in the right ventricle is usually increased as compared to the right atrium. Moreover, a further increase in oxygen content may be expected in the pulmonary arteries, coupled with systemic arterial oxygen desaturation. The oxygen saturations of the pulmonary arteries and systemic arteries may well differ, due to differential streaming. The systemic arterial oxygen saturation may actually be within "normal limits." Considerable difficulty arises in failure to identify correctly the location of the catheter tip when arterial areas are entered. The truncus can usually be entered, but its anomalous location and direction may be confusing if the defect is not suspected ahead of time. There is greater difficulty in entering the pulmonary arteries than in passing the catheter tip up into the aortic arch. In several cases diagnosed clinically but not verified by direct observation we have entered an arterial trunk from an anomalous position and have failed to enter the pulmonary arteries.

Confusion from catheterization, particularly in the cases with borderline systemic arterial oxygen saturation, centers around the exclusion of aortic-pulmonic defect, patent ductus arteriosus, or ventricular septal defect with marked pulmonary hypertension. D'heer and van Nieuwenhuizen[23] have described a method of identifying the first of these by passage of the catheter through the defect and then down toward the aortic valve, as well as upward into the arch of the aorta, with films being taken of the catheter in these positions. It is true that a significant increase in oxygen content in the right ventricle would tend to rule out an aortic-pulmonic defect. A nonreversing patent ductus arteriosus can be identified if the catheter is passed through it in typical fashion. A reversing patent ductus arteriosus can be identified by the difference in oxygen saturations of the right brachial and femoral arteries. An isolated ventricular septal defect can be ruled out if the catheter can be manipulated from the aortic arch to a pulmonary artery without a change from an arterial type of pressure tracing. The limiting factor in all of these situations is of course the frequent inability to direct the catheter tip into all of the desired structures. Dye-dilution technics might well be expected to supplement cardiac catheterization as a means of detecting right-to-left shunts in those cases where the shunt is too small to be seen on angiocardiography. Some of the foregoing clinical features are listed in table 6 for use in differential diagnosis. The presence of combined defects, such as patent ductus arteriosus with ventricular septal defect, increases the chances for diagnostic error.

Autopsy and Surgical Findings (table 5)

All but 2 of the autopsied cases had a truncus guarded by 3 semilunar cusps. The 2 exceptions

had but 2 cusps, but in each of these cases one of the cusps was an obvious fusion of 2 cusps. Clinical findings appeared to be unrelated to the type of origin of the pulmonary arteries, whether arising as separate vessels or as a common vessel. None of our cases had pulmonary arteries arising from opposite sides of the truncus. Instead, the vessels arose from the left posterior aspect of the truncus. Case 13 was an exception in this respect, the pulmonary arteries arising from the right posterior aspect of the truncus, but there was also dextrocardia and a left aortic arch in this case. Although the heart was not a true mirror image dextrocardia, it seems plausible to implicate inversion of the truncus structures.

Five of the 14 cases had associated noncardiac defects, but all of the latter were different.

Summary

Fourteen cases of true truncus arteriosus of type 1 (with 2 pulmonary arteries) are presented, with emphasis on the variation in clinical findings. Three lived to be 7 years or more of age. Growth retardation, respiratory infections, and dyspnea were common features. Cyanosis was not present in all cases. There was usually a precordial bulge, even in infancy. A systolic thrill and murmur along the left sternal border were typical, with occasionally a blowing diastolic murmur along the upper left sternal border in the older patients, but never a machinery murmur. No instances of a "split" pulmonic second sound were reported. Blood pressures were generally normal. The electrocardiogram usually showed right axis deviation and right ventricular preponderance, but the most consistent finding was peaking of the P waves. There was typically cardiac enlargement with an increase in the pulmonary vascular markings. The pulmonary artery segment was usually flat, but in some cases a "bulge" was formed by a left pulmonary artery, generally with a high take-off. A "shelf" was noted only once in the left anterior oblique view.

A "pure" and accentuated pulmonic second sound appears to be a cardinal diagnostic point. Angiocardiography, preferably biplane, is the most informative of the diagnostic procedures, though in cases where differential streaming results in a near normal systemic arterial oxygen saturation, this test, as well as conventional retrograde aortography, will fail to outline the defect. It is with cases in this group that the clinician is likely to make an erroneous diagnosis. Aortography, with injection of the contrast material through a catheter into the "ascending aorta." should be very informative under such circumstances. Dye-dilution technics combined with cardiac catheterization should also be very helpful.

The possibility of truncus arteriosus should be considered in all cases resembling "atypical" patent ductus arteriosus, aortic-pulmonic defect, and ventricular septal defects with marked pulmonary hypertension. A slight decrease in systemic arterial oxygen saturation and inability to enter the pulmonary arteries, together with a ready entry into the ascending aorta, should increase this suspicion. The finding of a large and actively pulsating "aorta" at fluoroscopy in a patient with the other cardiac catheterization findings of a ventricular septal defect and right ventricular hypertension is quite suggestive of a truncus arteriosus, since the aorta is invariably relatively small and inconspicuous in a patient with a left-to-right shunt due to isolated ventricular septal defect. Moreover, in a patient suspected of having a patent ductus arteriosus, especially if it is considered somewhat atypical and cardiac catheterization discloses right ventricular hypertension together with a left-to-right shunt at that level, the possibility of a truncus arteriosus must be considered.

Summario in Interlingua

Es presentate 14 casos de ver trunco arteriose, typo 1 (con 2 arterias pulmonar). In le presentation, le variabilitate del constatationes clinic es sublineate. Tres del patientes viveva a etates de 7 annos o plus. Retardo de crescentia, infectiones respiratori, e dyspnea esseva aspectos commun. Cyanose non esseva presente in omne casos. In le majoritate del casos un protrusion precordial esseva notate, mesmo in le infantia. Un fremito o murmure systolic al longo del margine sinistro-sternal esseva typic, con a vices un sufflante murmure diastolic al longo del margine supero-sternal

in le patientes de plus alte etates. Nulle rumor a machinas esseva notate. Nulle caso de "bifide" secunde sono pulmonic esseva reportate. Le pressiones sanguinee esseva generalmente normal. Le electrocardiogramma exhibiva usualmente deviation dextrorse del axe e preponderantia dextero-ventricular, sed le plus uniforme constatation esseva le appunctation del undas P. Allargamento cardiac esseva typic, con augmento del marcas pulmono-vascular. Le segmento del arteria pulmonar esseva usualmente platte, sed in certe casos un protrusion esseva formate per un arteria sinistro-pulmonar, generalmente a initio alte. Un "banca" esseva notate un sol vice, in le vista oblique sinistro-anterior.

Un "pur" e accentuate secunde sono pulmonic es apparentemente un puncto diagnostic cardinal. Angiocardiographia — preferibilemente biplan—es le plus informante manovra diagnostic, sed in casos in que fluxo differential resulta in quasi normal saturation oxygenic del arterias systemic, iste technica—si ben como le aortographia retrograde conventional —non pote succeder a definir le defecto. Il es in casos de iste gruppo que le clinico curre le plus grande risco de un diagnose erronee. Aortographia—con injection del substantia de contrasto via un catheter a in le "aorta ascendente"—pote devenir multo informative sub tal conditiones. Le mesmo vale pro technicas a dilution de colorantes in combination con catheterisation cardiac.

Le possibilitate de trunco arteriose deberea esser prendite in consideration in omne casos que resimila "atypic" patente ducto arteriose, defecto aorto-pulmonic, e defectos ventriculoseptal con marcate grados de hypertension pulmonar. Leve augmentos del saturation oxygenic in le sanguine arterial systemic e le impossibilitate de entrar in le arterias pulmonar combinate con facile accessibilitate del "aorta ascendente" pote servir a reinfortiar ille suspicion. Le constatation fluoroscopic de un grande "aorta" a pulsation active in un patiente qui exhibi le altere constatationes de catheterisation cardiac characteristic de un defecto ventricular e de hypertension dexteroventricular es un forte indication de trunco arteriose, proque le aorta es semper relativemente parve e inconspicue in patientes con derivation sinistro-dextere in consequentia de un isolate defecto ventriculo-septal. In plus, in un patiente in qui il existe le suspicion de patente ducto arteriose—specialmente si illo pare esser un pauco atypic e si le catheterisation cardiac revela hypertension dexteroventricular insimul con un derivation sinistro-dextere a ille nivello—le possibilitate del presentia de trunco arteriose debe esser prendite in consideration.

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Littman, D. S., Jeffers, W. A., and Rose, E.: The Infrequency of Myocardial Infarction in Patients with Thyrotoxicosis. Am. J. M. Sc. **233:** 10 (Jan.), 1957.

Although cardiac infarction has rarely been observed to occur in patients with active thyrotoxicosis, the authors present 3 such patients discovered during the past 4 years. The clinical course of the 3 patients did not reveal definitive differences between them and others who suffered cardiac infarction in the absence of thyrotoxicosis. The onset of infarction seemed to have been associated with a lesser severity of pain than usual in each of these 3 patients. With the advent of more effective medical measures for suppressing thyroid toxicity, it is conceivable that patients with coronary atherosclerosis and thyrotoxicosis may be relieved of their attacks of angina more readily, but may suffer cardiac infarction when thyroid toxicity is brought under control, unless steps are taken to avoid elevation of serum lipid levels. A further explanation for the rare coincidence of these 2 disorders is to be found in the work recently reported by Rowe et al. They found that the hypermetabolic state of thyrotoxicosis includes the myocardium. When patients were restored to the euthyroid state with treatment, the cardiac output, cardiac work, coronary blood flow, and myocardial oxygen consumption became normal, and the coronary vascular resistance increased.

HARRIS

Chest Pain with Inverted T Waves, Predominantly in Precordial Leads, as the Only Electrocardiographic Abnormality

By FRANK B. CUTTS, M.D., FRANK MERLINO, M.D., AND FREDERIC W. EASTON, M.D.

Sixty-nine hospitalized patients, who gave a history of "coronary" type chest pain appearing at rest and lasting at least 15 minutes, and whose electrocardiographic changes were limited to deeply inverted T waves predominantly in the precordial leads, were selected from a large series of patients. The hospital course and electrocardiographic changes of these patients were studied. After an average follow-up period of 4 years, approximately half the patients were still able to work. Postmortem studies on 11 patients revealed extensive sclerosis of the coronary arteries in all.

A CONSIDERABLE number of patients without typical acute myocardial infarction have a "coronary" type of chest pain at rest, with only an inversion of the T waves, particularly in the precordial electrocardiograms. In this paper we seek to clarify some of the diagnostic and prognostic features of this group by an analysis of 69 hospitalized patients with this combination of symptoms and electrocardiographic findings.

Patients with this type of chest pain fall into a group that, with rather fuzzy borders, lies intermediate between typical angina pectoris and acute myocardial infarction. This syndrome has been variously labeled as "coronary failure,"[1] "acute coronary insufficiency,"[2,3] "intermediate coronary syndrome,"[4] and "prodromal symptoms in myocardial infarction."[5] It is well recognized that patients with identical symptoms may demonstrate electrocardiograms clearly different from those with the precordial T-wave inversions described in this paper. There may be QRS abnormalities indicative of some degree of myocardial infarction; there may be a significant degree of S-T deviation, usually depression; and, indeed, the electrocardiogram may be entirely normal. Patients with these last 3 types of electrocardiograms are not considered here.

METHODS

All electrocardiograms with multiple precordial leads, taken prior to January 1, 1955, and classified in our files under the headings "acute anterior myocardial infarction" and "abnormal precordial T waves," were scrutinized. During this period the electrocardiographic diagnosis of acute anterior myocardial infarction was made in 784 patients. Tracings with recognizable QRS abnormalities, including bundle-branch block, intraventricular block, and the pattern of marked left ventricular enlargement (abnormally tall R waves in V_5 and V_6 with maximal T-wave inversions in these same leads) were excluded. From this relatively large group were selected, by consulting the clinical records, only those patients who gave a history of substernal pain occurring at rest and lasting approximately 15 minutes or longer. If hypertension was noted clinically, cases were included only if the electrocardiograms demonstrated considerable precordial T-wave inversion that had appeared since a previous record taken within 6 months, or if the T-wave inversions were shown to be transient by subsequent tracings. Patients on digitalis were excluded unless the T-wave inversions were clearly greater than could be reasonably attributed to this medication and were unaccompanied by significant sagging of the S-T intervals. Cases were omitted in which there was clinical evidence of pulmonary emboli, pericarditis, significant electrolytic disturbances, recent paroxysmal tachycardia, or myxedema. No instance of beriberi or the "juvenile pattern"[6] of precordial T-wave abnormality was included.

Within these limitations we were left with 69 cases for analysis.

RESULTS

Clinical Considerations. The pertinent clinical data are summarized in table 1. The ratio of males to females was somewhat less than the usual 3 or 4:1 noted in groups of patients with myocardial infarction. However, there were 14 males and only 1 female among those under 51 years of age; conversely, there were 8 females and only 2 males among those whose age was 71 or more. These figures clearly illustrate the tendency of coronary artery disease to become manifest in men at a younger age but our group

TABLE 1.—*Clinical Data*

Age (years)	Male	Female	Total
31–40	5	0	5
41–50	9	1	10
51–60	14	7	21
61–70	14	9	23
71–80	2	7	9
81–90	0	1	1
Total	44	25	69

	Number of patients	Per cent of total patients
Pre-existing angina pectoris	34	49
Pre-existing hypertension	37	54
Pre-existing diabetes mellitus	6	9
Time of onset of chest pain		
1 day or less	25	36
2–7 days	22	32
over 1 week	22	32
Duration of chest pain		
15 minutes	14	20
15–30 minutes	6	9
30–60 minutes	9	13
over 1 hour	35	51
unknown	5	7
Fever (over 100°)	12	17
WBC		
over 10,000	29	43
10,000 or less	39	57
Sed. rate (Wintrobe)		
over 20 mm./hr.	38	73
under 20 mm./hr.	14	27

is too small to permit any other firm conclusions.

About half the patients gave a history of pre-existing angina pectoris and an approximately equal number were observed at some time to have had hypertension, usually mild in degree or transient in duration. However, any patient observed at any time to have had a systolic blood pressure over 150 mm. or a diastolic pressure over 90 mm. was included under this heading. The onset of substernal pain appearing at rest occurred about equally 1 day or less, 2 to 7 days, or over 1 week prior to hospital admission. In about half the group the substernal pain was described as lasting over 1 hour. However, it often showed a tendency to wax and wane and seldom lasted over 4 hours. Moreover, the development of shock, gallop rhythm, or a pericardial friction rub was not observed, except with definite myocardial infarction, occurring later.

In 12 patients a temperature over 100 F. was noted during the first few days of hospitalization. Although this fever seldom lasted more than a day or 2 and did not exceed 102 F., it suggested the occurrence of some degree of myocardial necrosis. In all patients except 1, a white blood cell count was obtained and was elevated, rarely over 15,000, in somewhat less than half the group. When determined, the sedimentation rate was found to be elevated more often than not. These elevations of the sedimentation rate and the leukocyte count may indeed have reflected myocardial necrosis in some cases. The increase in the white blood cells was usually minor, however, and it has been demonstrated[7] that angina pectoris alone will elevate the sedimentation rate.

Forty-seven patients received bishydroxycoumarin (Dicumarol) during their hospital stay. However, only 17 of these had a sufficient amount of the drug to constitute reasonably adequate treatment (prothrombin time determinations of 30 per cent or less on at least half the tests performed after the second day of Dicumarol administration). Although our cases are too few to permit any definite conclusions, we could detect no appreciable differences in the clinical course between the groups receiving "adequate," "inadequate," or no Dicumarol therapy. We have no data in this series concerning longer term Dicumarol therapy.[8, 9]

Electrocardiograms. In table 2 are summarized some of the electrocardiographic data. There was no evident relationship between the degree of precordial T-wave inversion and the clinical course. In slightly less than half the patients electrocardiograms were taken with sufficient frequency to permit some estimate of the duration of the precordial T-wave inversion. In 18 cases the T-wave had returned to normal by the end of 2 months. Conversely, in none of the 7 patients dying within the first year was a normal electrocardiogram obtained at any time. The last tracing available for each patient was normal in about one third of this series.

Follow-Up. The status of each patient when last seen or heard from is listed in table 3.

TABLE 2.—*Electrocardiographic Data*

	Number of patients	Per cent of total patients
Degree of maximum T-wave inversion		
less than 5 mm.	29	42
5–10 mm.	29	42
over 10 mm.	11	16
Duration of T-wave inversion		
less than 1 month	10	34
1–2 months	8	27
2–6 months	7	24
over 6 months	4	14
Last electrocardiogram		
normal	24	35
myocardial infarction	15	22
inverted T waves	25	36
* miscellaneous	5	7

* Three bundle-branch block and 2 with depressed S-T segments.

TABLE 3.—*Clinical Course and Follow-up Data*

Clinical course	Number of patients	Per cent of total patients
Recovery	18	26
Myocardial infarction	17	26
Persisting angina	24	34
Congestive failure	3	4
Died of miscellaneous causes (5 cancer, 1 postoperative, 1 cerebral thrombosis)	7	10

Duration of follow-up (years)	Dead	Disabled	Active
0–1	7	0	0
1–2	3	1	3
2–3	3	1	9
3–4	5	2	7
4–5	4	2	4
5–6	0	1	5
over 6	2	3	7

TABLE 4.—*Time and Cause of Death*

Time between hospitalization and death (years)	Number of deaths	Cause of death		
		Myocardial infarction	Cancer	Miscellaneous
Less than 1	7	6	0	1 (coronary sclerosis)
1–2	3	3	0	0
2–3	3	0	0	1 (cerebrovascular accident) 2 (unknown cause)
3–4	5	1	2	1 (congestive heart failure) 1 (unknown cause)
4–5	4	1	2	1 (sudden death)
5–6	0	0	0	0
Over 6	2	0	1	1 (rupture urethra)

Eighteen patients recovered sufficiently to be without symptoms. The cases listed as "active," almost exactly half the total group, were working or able to do at least light work even though some had mild to moderate angina pectoris.

Deaths. During the follow-up period there were 24 deaths, of which 14 (20 per cent of the entire group) were known to be due to heart disease (table 4). Seven of the 14 cardiac deaths occurred during the first year. Thereafter the hazard of death from cancer (5 cases) approximated that from heart disease. In the 14 patients who died of heart disease, the incidence of angina, hypertension, and diabetes, the duration of pain, the degree of T-wave inversion, and the occurrence of fever, leukocytosis, and elevated sedimentation rates were about the same as in the entire series. However, in spite of the relatively high number of older women in the entire group, 11 of the 13 known to have had cardiac deaths were males, further illustrating the comparative vulnerability of men to this disease.

Autopsies. Eleven autopsies were obtained in the 24 patients who died. The most striking finding was the high degree of narrowing and atheromatosis of the coronary arteries (table 5). We had an opportunity to examine personally almost all of these hearts and can corroborate this finding. Three hearts revealed no myocardial lesion grossly, although 2 of these showed small focal areas of fibrosis microscopically. One heart showed streaks of fibrosis widely distributed throughout the midportion of the left ventricular myocardium, 9 years after the patient's episode of pain. One heart exhibited a small healed posteroseptal infarct. The remaining 6 specimens all showed extensive infarcts, usually acute, that could clearly be related to episodes of prolonged pain occurring after the original episode for which they were included in this study. Of these 6 hearts, one had an old septal infarct, which

TABLE 5.—*Postmortem Findings*

Duration of chest pain	Interval between onset of chest pain and death	Heart weight (Gm.)	*Degree of coronary sclerosis			Heart muscle		Noncardiac findings
			LAD	LC	R	Gross	Microscopic	
20 mins.	3 months	340	X	N++++	N++++	Old and recent anterior infarction; old posterior infarction	Acute and subacute infarction	
Several hours	6 years	360	N+++	N++++	N++++	Negative	Negative	Cancer of bladder
Several hours	1 month	390	N+++	N+++	N+++	Negative	Fibrosis indicating healed infarction	
3 hours	2 weeks	430	N+++	N+++	N+++	Negative	Focal areas of necrosis	
2 hours	9 years	350	N++++	N+++	N+++	Streaks of fibrosis in middle of wall of lt. ventricle	Areas of fibrosis	Ruptured urethra (postop)
1 hour	6 weeks	690	X	N+++	X	Extensive acute infarction and some patchy fibrosis	Acute infarction and patchy fibrosis	
6 hours	5 years	460	N++++	N+++	N+++	Healed posteroseptal infarction	Rt. ventricle almost replaced by tumor, fairly extensive fibrosis of lt. ventricle	Cancer of thyroid with extensive metastases
4–5 hours	3 years	660	X	X	X	Old posterior myocardial infarction, patches of fibrosis anteriorly	Same as gross	
Several hours	21 months	510	X	X	N++	Recent anterior and old septal infarctions	Same as gross	
3–4 hours	5+ years	400	X	N++	N++	Extensive recent ant. infarction with rupture	Same as gross	
Several hours	2 weeks	490	X	N++	N++++	Extensive recent ant. infarction with pericarditis and mural thrombus	Same as gross	Bronchopneumonia

* X = lumen occluded, N = lumen narrowed from 10–15 per cent (+) to 75–90 per cent (++++), LAD = left anterior descending coronary artery, LC = left circumflex artery, R = right coronary artery.

may have occurred at the time of the patient's original chest pain, and another, in addition to the acute infarct, had patchy fibrosis microscopically, which may well have occurred with the initial episode of chest pain. The myocardial lesions were thus rather variable, and the one common denominator was quite clearly the high degree of coronary artery narrowing.

ILLUSTRATIVE CASES

Case no. 37. D. T., a 47-year-old white man, was admitted to the Jane Brown Memorial Hospital on July 10, 1952. Four years previously he had de-

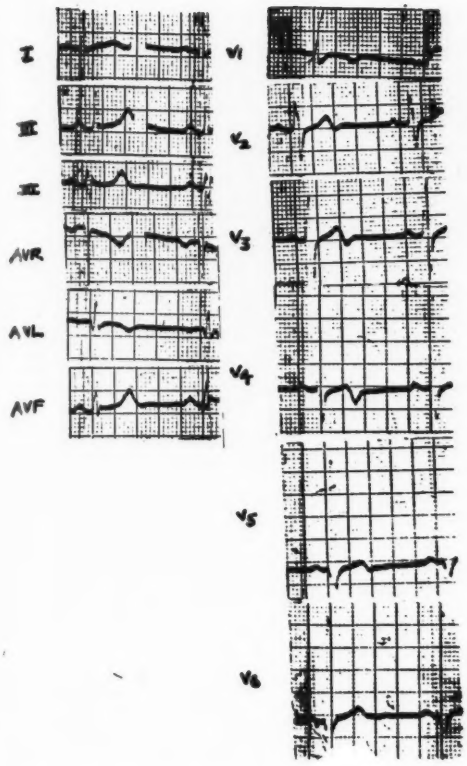

FIG. 1. Case no. 37. Electrocardiogram, 2 weeks before death. Note the terminal inversion of the T waves in leads V_2 through V_5 without other significant abnormality.

veloped typical angina, which improved markedly on a low-fat diet and a subsequent weight loss of 20 pounds. He had no further cardiovascular symptoms until July 9, 1952, when he noted the sudden onset of dull substernal pain radiating into the left arm and lasting some 3 hours.

The temperature was 98.6 F., the pulse 80, and the blood pressure 120/70. The heart was normal in size, sounds, and rhythm. There was no evidence of congestive failure. An electrocardiogram (fig. 1) revealed no QRS or S-T abnormalities. T waves in aV_L, however, were inverted, as were the terminal portions of the T waves in leads V_2 through V_5. Laboratory data included a negative urinalysis, sedimentation rate of 10 mm. per hour, white blood count of 10,600 with 74 per cent polymorphonuclear cells, and a blood cholesterol of 193 mg. per cent.

The patient was treated with rest and Dicumarol. After the second hospital day, 7 of 10 prothrombin activity determinations were 30 per cent or less. He remained afebrile and appeared to be recovering satisfactorily until the morning of July 24, 1952, when he awoke at 3:30 complaining of substernal discomfort that lasted about 2 hours and required 2 injections of meperidine for relief. Some 3 hours after the onset of pain, however, he suddenly died.

At necropsy, the heart weighed 430 Gm. Serial sections through the myocardium were negative on gross inspection. The coronary arteries revealed 3 to 4 plus sclerosis with markedly narrowed, but not occluded lumina. Sections through the anterior left ventricle revealed several scattered, irregularly shaped, focal areas that were pale-staining and composed of remnants of myocardial fibers and small amounts of granulation tissue with congested capillaries and small numbers of round cells. These areas were surrounded by myocardial fibers of normal appearance. The coronary vessels revealed large atheromatous plaques that reduced the lumina to 10 to 20 per cent of normal. No subendothelial hemorrhages were seen (figs. 2 and 3).

Case no. 39. J. B., a 64-year-old white man, was admitted to the Rhode Island Hospital on January 3, 1942. Previously, while walking home, he suddenly experienced epigastric and lower substernal oppression accompanied by dyspnea, perspiration, and collapse. His pain lasted 2 to 3 hours.

Physical examination revealed a cyanotic, obese man breathing rapidly with audible wheezing. Temperature was 98 F., pulse 120, respirations 35, blood pressure 158/80. Rales and rhonchi were present bilaterally. The heart was slightly enlarged, with normal sounds. For the first 3 days his temperature reached 101 F. rectally. He made an uneventful recovery and was discharged after 17 days. Electrocardiograms (fig. 4) showed only T-wave changes with a maximum inversion of 17 mm. in lead CF_4 on January 5, 1942. Other laboratory data included a negative urinalysis, a blood glucose of 104 mg. per cent and a blood urea nitrogen of 21 mg. per cent. On the third hospital day, a white blood count was 11,200 with 81 per cent polymorphonuclear cells.

During 1943 the patient suffered 2 minor cerebrovascular accidents. In 1948 he was re-admitted because of polyuria, polydipsia, and weakness of both legs. With control of his newly discovered diabetes he improved. Examination of the heart was negative. The electrocardiogram was now normal (fig. 4).

In 1950 he re-entered the Rhode Island Hospital because of mild hematemesis. X-ray studies showed a duodenal ulcer. On April 30, 1951, he was hospitalized for the last time because of urinary incontinence. Since his previous hospital admission he had been digitalized. He denied angina but claimed some palpitation, exertional dyspnea, and occasional ankle swelling. Heart examination showed a grade III harsh precordial systolic murmur; by x-ray the heart measured 12.9 cm. and the intrathoracic diameter was 25.1 cm. He died of urinary sepsis 5

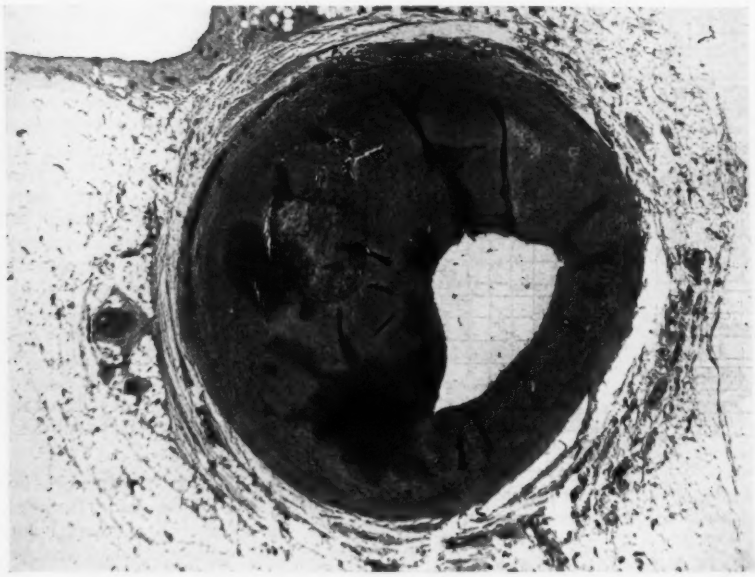

FIG. 2. Case no. 37. Photomicrograph of cross section of the right coronary artery (× 60). Note the marked, asymmetric thickening of the intima. The dark, irregular areas within the intima represent calcification.

days after cystoscopy. Electrocardiograms (fig. 4) showed low, but upright T waves in V_4 to V_6.

Autopsy revealed the primary cause of death to be urethral rupture with pelvic abscess formation. The heart was normal grossly except for 4 plus coronary sclerosis and streaks of fibrosis in the midwall of the left ventricle. The heart weighed 350 Gm. Microscopically small bands of fibrosis between myocardial fibers were noted.

DISCUSSION

Three aspects of the problem presented by the type of patient under consideration here may merit further comment.

Prognosis. Some authors[3, 10] have commented on the relative benignity of this syndrome. For example, Barker[11] described similar cases and stated that the prognosis is invariably good. However, Levy[12] pointed out the considerable hazard of sudden death in patients with similar symptoms and electrocardiographic findings, and Mounsey[5] indicated that at times this clinical picture may represent the prodromal phase of acute myocardial infarction. Since 7 of our patients died within 1 year after the onset of this syndrome, we are inclined to be less sanguine than some regarding the short-term prognosis. After the first year the hazard of death from heart disease seems to diminish appreciably.

Pathologic Considerations. In an excellent study leavened by the lighter touch, Pruitt and co-workers[2] considered the clinical and pathologic implications of deeply inverted T waves in the midprecordial leads. They found that patients selected only on the basis of this type of electrocardiogram showed a high incidence of severe coronary insufficiency or myocardial infarction. In their 9 autopsied cases healed subendocardial infarction was found in 8. Although all 11 of our autopsied patients showed advanced narrowing of the coronary arteries, in only 3 instances were grossly recognizable healed infarcts evident in multiple sections of the heart, cut transversely in the plane of the atrioventricular groove. Since many, if not all, of our surviving patients presumably have a similar advanced degree of coronary artery narrowing (3 of our autopsied cases died of causes other than heart disease), one is compelled to marvel at the efficacy of the intercoronary anastomotic circulation[13] that seems to develop as the subjects recover or improve.

Anticoagulant Therapy. Some investigators[8,

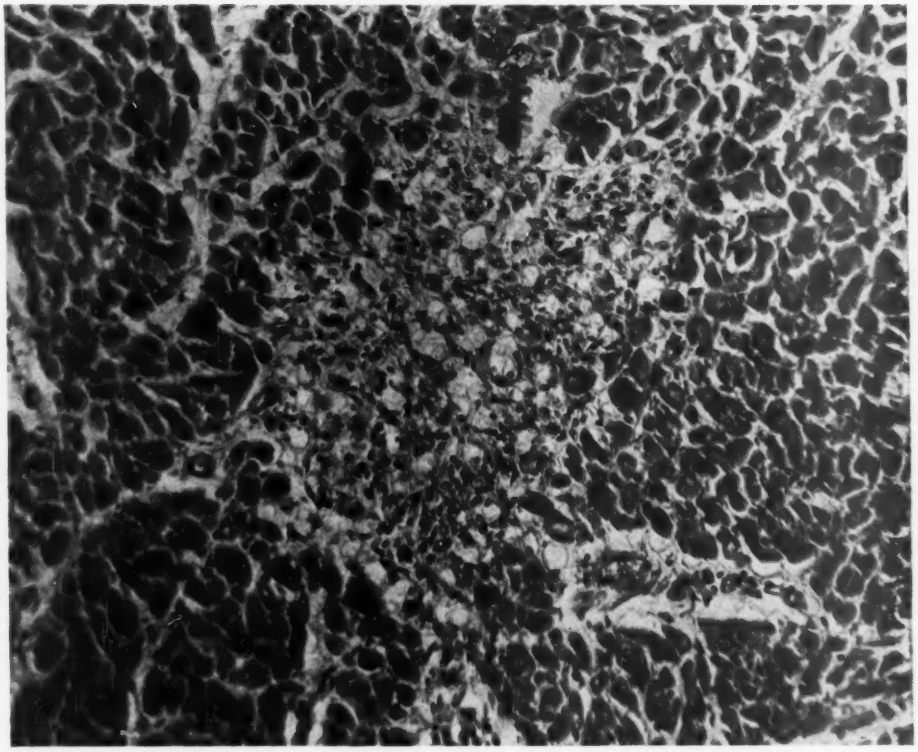

FIG. 3. Case no. 37. Photomicrograph of section from the left ventricle (× 400). The irregular, roughly elliptical, area in the center of the field represents focal necrosis of muscle cells without much loss of residual stroma. Some granulation tissue and small numbers of round cells are present. The surrounding myocardium is normal.

[9, 14] recommend the use of anticoagulants in the type of cases considered here; others[3, 4] do not believe they are indicated. Our own data are not very helpful on this point. However, since only 2 of our patients died during their original hospitalization and of these 1 was on adequate Dicumarol therapy, the immediate value of anticoagulants in this type of case remains uncertain. Certainly this type of therapy does not appear to lessen the hazard of sudden death nor does it prevent myocardial infarction with any great assurance.[15] As indicated in table 4, since the hazard of subsequent myocardial infarction is appreciably greater in the first year after the acute episode of pain, anticoagulant therapy, if undertaken, should probably be prolonged, perhaps following the recommendations of Thompson,[8] who continues treatment until the electrocardiogram is normal and angina, if present, is no worse than before the acute episode.

SUMMARY

This study is concerned primarily with the clinical course of 69 hospitalized patients with chest pain at rest and with normal electrocardiograms except for deep inversion of the T waves, particularly in precordial leads.

In a small number of cases there was clinical evidence of a minor degree of myocardial necrosis. More commonly such evidence was lacking. In about one third of the entire group, the electrocardiogram returned to a normal configuration. After an average follow-up period of about 4 years, half the total group were either working or were active in their homes and communities.

There were 24 deaths, of which 14 were

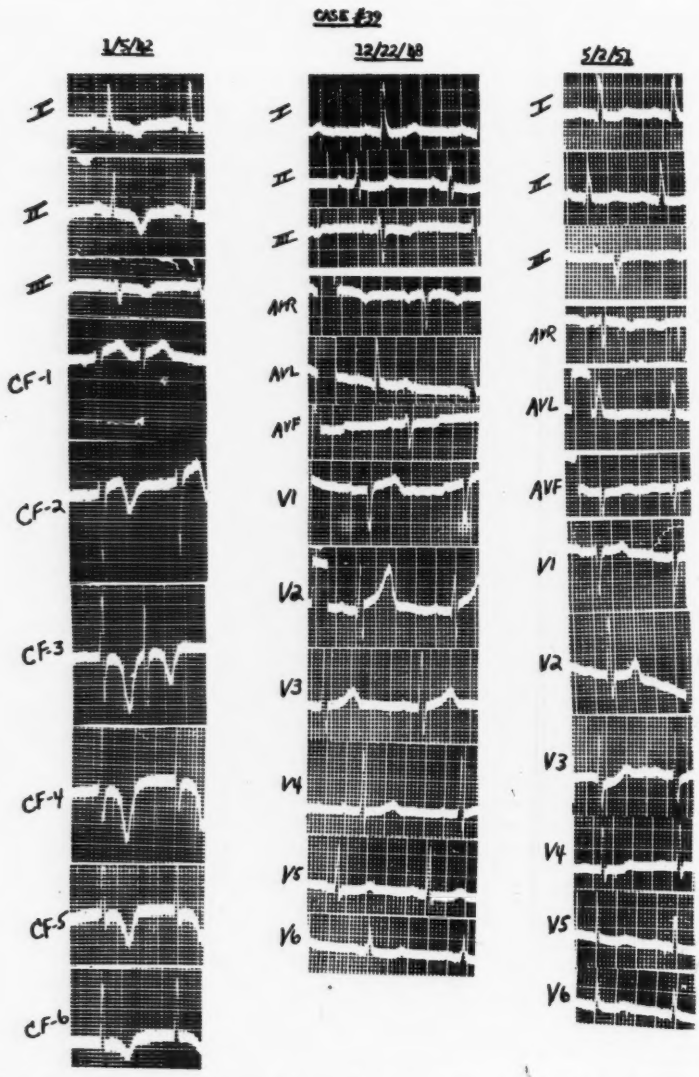

FIG. 4. Case no. 39. Electrocardiograms: January 5, 1942. Note the normal QRS complexes and the deep inversion of the T waves in the precordial leads. December 22, 1948. The electrocardiogram is now normal. May 2, 1951. Taken 6 days before death, QRS complexes are unchanged and the T waves, although lower, are not beyond normal limits.

known to be due to heart disease, chiefly myocardial infarction. Seven of the cardiac deaths occurred in the first year of follow-up. Eleven patients came to autopsy. In all instances there was a high degree of atheromatous narrowing of the coronary arteries. Grossly visible myocardial lesions, which could reasonably be correlated with the episodes of pain under consideration here, were usually absent. In a few instances small healed infarcts were noted.

We are rather skeptical of the value of Dicumarol in the type of case under discussion, but our data permit no definite conclusions. If

used, it should probably be continued for several months.

Acknowledgment

We are indebted to Dr. George F. Meissner, Associate Pathologist, Rhode Island Hospital, for taking the photomicrographs shown in figures 2 and 3, and for assistance in their interpretation.

Summario in Interlingua

Iste studio es concernite primarimente con le curso clinic de 69 patientes hospitalisate con dolores thoracic in stato de reposo e con electrocardiogrammas normal a parte le presentia de un profunde inversion del undas T, particularmente in derivationes precordial.

Un parve numero de casos exhibiva signos clinic de minor grados de necrosis myocardial. Plus communmente, tal signos esseva absente. In circa un tertio del gruppo, le electrocardiogrammas retornava a configurationes normal. Post un periodo medie de 4 annos de observation consecutori, un medietate del gruppo total travaliava o esseva active in lor domicilios e communitates.

Occurreva 24 mortes. Dece-quatro de istos esseva cognoscitemente causate per morbo cardiac, principalmente infarctos myocardial. Septe del mortes cardiac occurreva durante le prime anno del observation ulterior. Dece-un patientes esseva necropsiate. In omne iste casos, un alte grado de restriction atheromatose del arterias coronari esseva constatate. Lesiones myocardial de visibilitate macroscopic que se correlationava plausibilemente con le episodios de dolor hic considerate esseva usualmente absente. In un basse numero de casos, parve e curate infarctos esseva notate.

Nos es satis sceptic quanto al valor de Dicumarol in le typo de caso sub discussion, sed nostre datos non permitte le formulation de conclusiones definite. Si usate, il es probabile que le droga deberea esser continuate durante plure menses.

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Stimulation of Interarterial Coronary Anastomoses by Experimental Acute Coronary Occlusion

By MILTON H. PAUL, M.D., LEONA R. NORMAN, M.D., PAUL M. ZOLL, M.D., AND HERRMAN L. BLUMGART, M.D.

"Hence it sometimes happens that, when the lumen of some artery has been too long obstructed or ligated, the blood busies itself in opening a wider channel for its passage in this vessel, must drive and buffet all the more into the next ones, until it has considerably dilated them to give itself room."[1]

The development of interarterial coronary anastomoses may exert a profound influence on the clinical course of angina pectoris, coronary failure, and acute myocardial infarction. Earlier studies have shown that marked narrowing of a coronary artery produces rich intercoronary anastomotic communications. The present study is designed to determine whether acute occlusion of a coronary artery in a previously normal heart also leads to the development of a collateral circulation and what length of time is necessary to establish such a collateral circulation.

FOLLOWING acute coronary occlusion, the infarcted myocardium is bordered by a zone of injured tissue that may undergo either necrosis or recovery. Bed rest or marked restriction of effort is prescribed after acute myocardial infarction to reduce the work of the heart, to minimize the size of the infarct, to favor recovery of the injured myocardial tissue, and to lessen the liability of cardiac rupture, congestive heart failure, and arrhythmia. According to previous experimental studies in the domestic pig,[2, 3] 12 or more days of 75 per cent narrowing are required to produce sufficiently rich intercoronary anastomotic communications to protect the myocardium from damage and to permit survival when the coronary circulation is subsequently challenged with an acute complete occlusion.

The present study was undertaken to learn (1) whether acute occlusion of a coronary artery in a previously normal heart leads to the development of a collateral circulation, just as marked narrowing does, and (2) the length of time necessary to establish such a collateral circulation.

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This investigation was aided by research grants from the National Heart Institute, U.S. Public Health Service (H-2208), and from the Massachusetts Heart Association.

METHODS

As in the previous studies on the effect of acute narrowing on the production of larger intercoronary collateral channels, the domestic pig was chosen as the experimental animal because pig hearts ordinarily do not show interarterial coronary anastomoses when injected with lead-agar mass.[2-4] In the normal dog, grossly visible interarterial communications, 100 microns or larger in diameter, were often demonstrated by this injection technic.[3-5]

Experimental Technic

Young pigs weighing 5 to 10 Kg. received 0.5 mg. of atropine sulfate preoperatively. Endotracheal ether anesthesia was employed. The heart was exposed by an incision through the third or fourth left intercostal space and the pericardium was opened. The left circumflex artery or one of its primary branches (table 1) was carefully dissected from its bed and a double ligature was passed around it and tied. Our previous studies in the pig demonstrated that acute occlusion of any of the 3 main coronary arteries near their origin uniformly resulted in death.[3, 4] In all the experiments of the present study, therefore, the left circumflex artery near its termination or one of its larger primary branches was selected for ligation. After various intervals (table 1) the pigs were sacrificed and the coronary arteries were examined post mortem with the injection plus dissection technic. The left anterior descending, the left circumflex, and the right coronary arteries were each individually cannulated via the aortic coronary ostia. The usual lead-agar mass was used—colored blue for the left descending, red for the right coronary, and yellow for the left circumflex coronary arteries. In order to fill any interarterial communications more completely, the technic of

TABLE 1.—*Extent of Anastomisis after Ligation of Left Circumflex Coronary Artery*

No.	Main stem or branch	Survival after ligation (days)	Anastomosis*	Infarction
1	M	1†	0	+
2	M	4†	0	+
3	B	4†	0	+
4	M	1	0	+
5	B	1	0	+
6	M	1	0	+
7	M	2	2+	+
8	M	2	3+	+
9	M	4	2+	+
10	M	4	3+	±
11	M	7	0	+
12	M	7	3+	+
13	M	10	2+	+
14	B	11	0	+
15	M	11	3+	+
16	B	17	0	+
17	M	18	2+	+
18	B	21	3+	+
19	M	23	3+	+
20	M	23	3+	+
21	B	25	3+	+
22	B	28	2+	+
23	M	29	1+	+

M = main stem of left circumflex coronary artery near terminal end.

B = branch of left circumflex coronary artery near terminal end.

* Anastomisis is graded from 0 to 3+.

† Hours.

injection was slightly modified by application of positive and negative pressures of 150 mm. Hg to the 3 cannulas in all possible combinations, with final application of positive pressure. The injection mass introduced in this manner into each of the 3 major coronary arteries in the hearts of normal pigs has previously been shown uniformly not to fill the smaller arteriolar vessels between 10 and 50 μ in diameter, and not to reach the capillary bed or the venous tree at all.[2-6]

Results

Normal and Control Groups

In 158 of 161 *normal* pig hearts no interarterial coronary anastomotic connections were found. In 2 hearts superficial anastomosing twigs were faintly outlined with injection mass; in only 1 normal control heart was there abundant intercoronary anastomosis such as seen after marked narrowing or complete occlusion (see below). Thus, the natural or spontaneous incidence of anastomoses of any degree in this series is 2 per cent.

In a second group of surgical *control* experiments 17 pigs underwent anesthesia or surgery but died or were sacrificed within 24 hours of the surgical procedure. In 11 instances the vessel was not tied or the animal did not survive the ligation. In 6 of the animals ligation of the left circumflex coronary artery was accomplished; however, since the animals died within 1 to 24 hours of ligation, they are included in this control group. These 6 animals also are listed in the table among the 23 animals in whom the left circumflex coronary artery was ligated (nos. 1 to 6, table 1). Slight anastomoses (1+) were found in only 1 of these 17 animals. Figure 1 shows the usual pattern of absent anastomosis in a control animal that died 4 hours after the left circumflex coronary artery was ligated; the peripheral segment of the vessel remained uninjected.

Intercoronary Anastomoses after Acute Coronary Arterial Occlusion

The table lists 23 animals that survived acute ligation of the left circumflex coronary artery. Of 17 animals who survived from 2 to 29 days after acute occlusion (nos. 7 to 23, table 1), abundant collateral circulation was observed in 13 (77 per cent). The segments of left circumflex coronary artery distal to the occlusion were filled with mass by way of interarterial anastomoses from the right coronary artery, the left anterior descending, or the left circumflex artery proximal to the tie. These anastomoses did not develop indiscriminately or diffusely in the coronary tree but in general bordered the infarcted area. The occurrence of extensive anastomoses in 77 per cent of the hearts in this group differs significantly from the incidence of slight anastomosis of only 2 per cent in the hearts from normal control pigs and from those surviving less than 2 days. Figure 2 shows rich anastomoses in the peripheral segment of the left circumflex artery (graded 3+) in a pig that was sacrificed 4 days after coronary artery ligation. In 3 animals surviving 7, 11, and 17 days (no. 11, 14, and 16

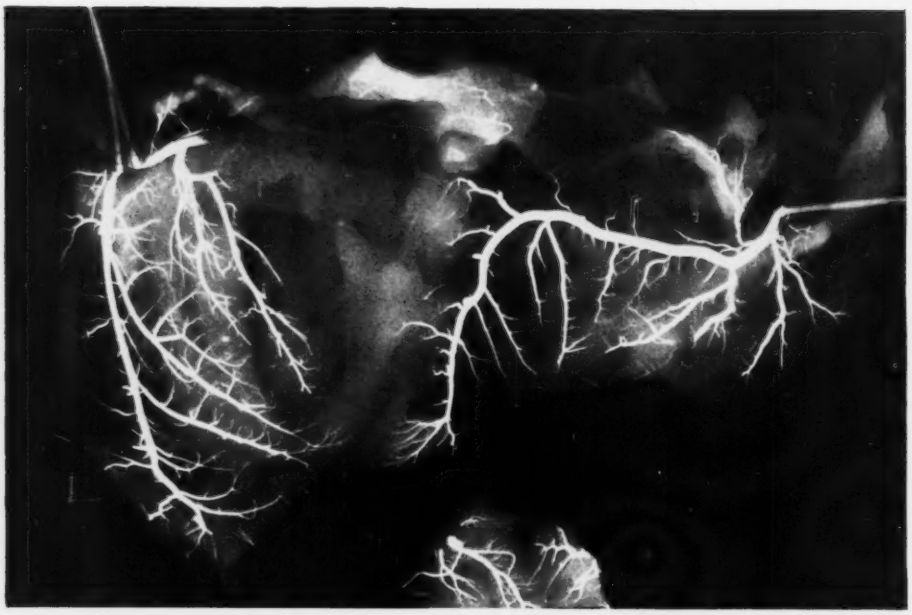

FIG. 1. Roentgenogram of injected and unrolled heart of pig no. 2 that died 4 hours after ligation of the left circumflex coronary artery. The peripheral portion of the vessel is uninjected (0 anastomoses). The arrow shows the point of ligation of the left circumflex coronary artery.

respectively) after occlusion, anastomotic channels were absent; the explanation for this failure of anastomosis to develop is not clear. We are not cognizant of an error in the technic of coronary artery ligation or faulty postmortem injection of these hearts. One can only conjecture that occasionally the area of infarction by chance completely involves all those vessels that provide the source for the development of such intercommunications. Such occasional exceptions occurred in previous similar studies by us[3, 4] and others.[7, 8] It is to be noted also that there was no apparent relation between the length of survival after occlusion and the abundance of the anastomotic channels. Thus, in 2 animals surviving 18 and 29 days, the extent of the anastomoses was moderate and slight (fig. 3), respectively, whereas in animals no. 8 and 10, who survived 2 and 4 days (fig. 2), the anastomoses were marked.

DISCUSSION

The results of the present study are in harmony with our previous observations regarding the characteristics of intercoronary communications. In the normal heart of the pig, dog, and man, fine interarterial coronary communications may be demonstrated by the ready passage of colored watery solutions or suspensions like india ink from one coronary artery to the other coronary arteries and their branches. These normal, anatomically demonstrable communications do not protect the myocardium from infarction when a coronary artery is occluded suddenly. They are therefore not of important functional significance, and the coronary arterial system may be regarded in these 3 species as an end-arterial system from the functional or physiologic standpoint.[5, 9] Larger interarterial communications, which are demonstrable by the Schlesinger technic, are present in 9 per cent of *normal* human hearts from patients without anemia.[6] In the pig, however, only 3 of 161 hearts examined have shown anastomoses; in 2, they were very slight. We can therefore be confident that the anastomoses observed in the present study

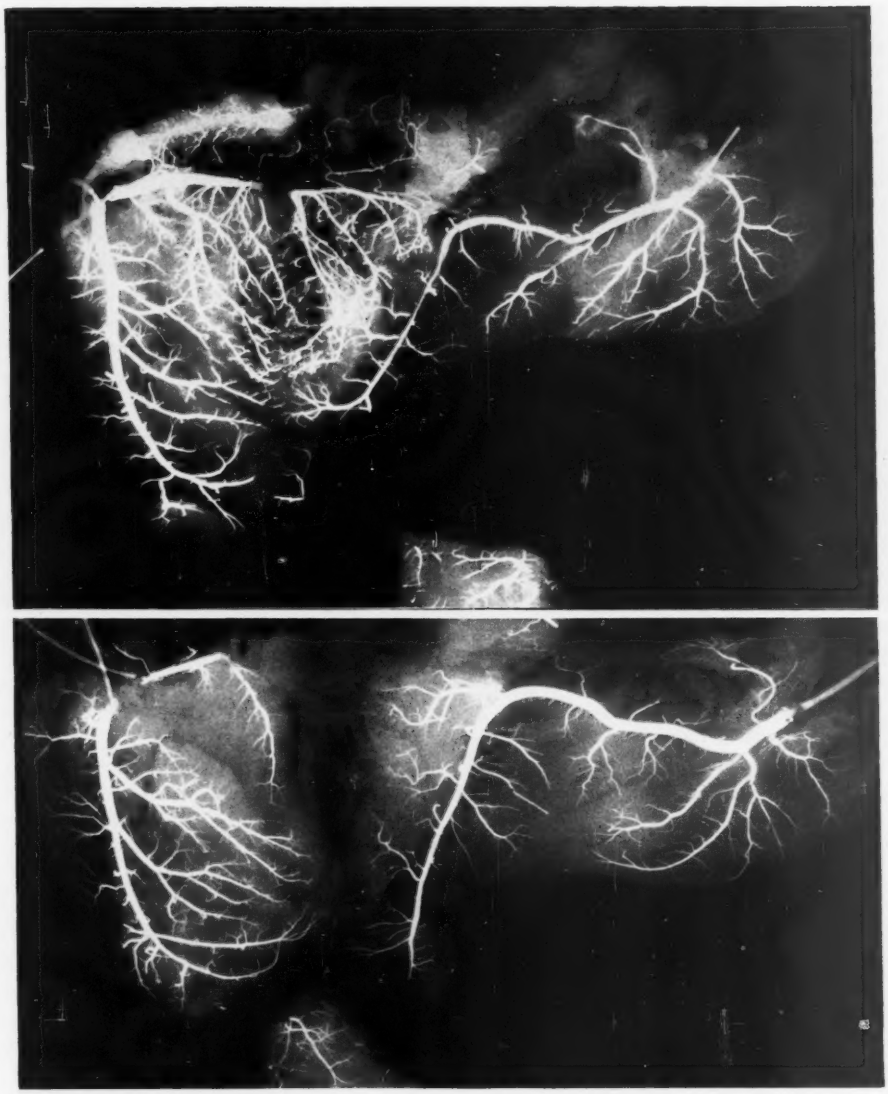

FIG. 2 *Top.* Roentgenogram of injected and unrolled heart of pig no. 10 that was sacrificed 4 days after ligation of the left circumflex coronary artery. The site of ligation (*arrow*) is well seen as an interruption of the injection mass, which fills the peripheral portion of the vessel by rich collateral vessels (3+ anastomosis) below the black rod.

FIG. 3 *Bottom.* Roentgenogram of injected and unrolled heart of pig no. 23 that was sacrificed 29 days after ligation of the left circumflex coronary artery (*arrow*). Only slight filling of some terminal twigs of the left circumflex artery was found on dissection (1+ anastomosis) and is seen on the film just below the black rod.

were not normally present and were consequent to the experimental procedure.

These intercoronary arterial anastomoses have engaged the interest of investigators because of their important function, after marked narrowing or complete occlusion of a coronary artery, in supplying blood from neighboring arteries to the capillaries and tissues of an infarcted or potentially infarcted area. The classic observations of Gregg and his associates[10-12] demonstrated that the blood delivered through these channels is arterial in nature and derived from the intact coronary arteries. Indeed complete occlusion of a main coronary artery gradually accomplished in successive stages was often not accompanied by myocardial infarction in the dog. Similar experimental observations were made by Blum, Schauer, and Calef,[13] by Burchell,[14] and by us.[3] The clinical counterpart of these experiences, i.e., the occurrence of complete coronary artery occlusions without myocardial infarction, has been noted by Saphir and his associates,[15] by Bean,[16] and by ourselves.[6] Recently, however, Snow, Jones, and Daber[17] have questioned the efficacy of the collateral vessels in preventing myocardial necrosis completely. They always found gross myocardial infarction of some extent in association with occlusions, although often considerably smaller than might otherwise have been expected. Since their observations were made in a series of 25 patients limited to those with clinical manifestations of coronary disease, instances of complete protection from infarction may well have been eliminated from consideration at the outset by the method of selection. In any event there is no question about the development of intercoronary anastomoses and their importance in ameliorating the consequences of coronary artery occlusion.

In the present study, as in our other studies, the injection mass never traversed pericardial adhesions to adjacent structures such as the venae cavae, the aorta, the pulmonary vessels, and the reflections of the parietal pericardium, despite the presence of fine extracardiac communicating vessels that may be demonstrated anatomically by the injection of india ink or similar suspensions. Similarly, if coronary-luminal communications of smaller size are present, they are like the normal fine interarterial coronary and extracardiac communications in that they are of little functional significance in safeguarding the myocardium after acute coronary occlusion.

Our previous studies showed early development of collateral circulation within 2 days in response to marked narrowing, but 12 or more days were generally necessary for the evolution of a rich anastomotic circulation that was functionally adequate to protect the heart from sudden, superimposed complete occlusion.[3, 4] The interval of 2 days required for the development of anastomoses in the present studies of occlusion is compatible with the previous observations after narrowing.

Although the results of this study demonstrate conclusively that increased collateral channels develop between unoccluded arteries and the occluded segment of another artery within 2 days, one cannot conclude that the collateral channels have reached their maximum development by that time. Donald and Essex,[7] using a barium-gelatin mixture to inject the dog heart after gradual occlusion of the right coronary artery close to the aorta, found that a postligation period of over 3 weeks was necessary for the evolution of a rich anastomotic circulation. Incomplete filling of the occluded artery was found in hearts examined after injection of the barium-gelatin material 1, 4, 9, 14 and 22 days after ligation of the right coronary artery at its origin. The longer time required for demonstration of collateral channels in their experiments may be due to differences in the injection mass, the site of the arterial ligation, species differences, and different criteria for demonstration of anastomotic injection in the 2 studies. It was shown by pathologic examination of the heart that sufficient retrograde flow occurred early to save some of the myocardium from necrosis.

The technic used in the present study of complete nonlethal ligation of a small branch of a coronary artery is better suited to the study of effects of drugs and various agents upon the development of intercoronary anastomoses than the technic of marked narrowing of a large vessel with subsequent ligation. It is

simpler and easier technically, obviates the major variable that is difficult to control (degrees of narrowing), and gives a higher per cent of control figures for comparison.

The relations of angina pectoris, coronary failure, and acute myocardial infarction to coronary arterial narrowing and occlusion and the development of collateral vessels in human hearts have been the subject of previous communications by us. We have reviewed our series of human hearts injected by the Schlesinger injection plus dissection method but have not found any exact clinical counterpart of the above described experimental situation: we have found no instance in which an acute coronary occlusion occurred in the presence of an otherwise normal coronary arterial tree; in every instance areas of moderate or marked narrowing were evident in other areas of the coronary arterial tree. Thus we are unable directly to extend these experimental findings with the present clinical autopsy material of more than 1000 hearts. Nevertheless, the observations of the present study in the uncomplicated experimental situation are valuable for orientation in clinical cases where acute complete occlusion occurs in hearts with varying degrees of narrowing.

In coronary artery disease extensive narrowing of the coronary arterial tree might preclude the development of a steep pressure gradient between neighboring uninvolved vessels. The derivation of collateral blood supply from such arteries following acute coronary occlusion in the human heart might then be expected to require a somewhat longer interval than the 2 or more days of the present experimental study. Moreover, the occasional heart observed in this and other series of animals in which much longer times are necessary to establish a rich collateral blood supply emphasizes the importance of bed rest and reduced activity for many weeks after acute myocardial infarction.

Summary

In a control series of 161 normal pig hearts only 3 hearts (2 per cent) were found to have intercoronary anastomotic connections by a technic of injection plus dissection of the coronary arteries with lead-agar mass.

In contrast, of 17 animals who survived from 2 to 29 days after acute coronary occlusion, abundant collateral circulation was observed in 13 (77 per cent).

These studies indicate that a significant intercoronary collateral circulation can develop within 2 days after acute coronary ligation.

Summario in Interlingua

In un serie de controlo de 161 normal cordes porcin solmente 3 (2 pro cento) revelava le presentia de anastomotic connexiones intercoronari. Le technica usate esseva dissection post injection de un massa de agar a plumbo in le arterias coronari.

Del altere latere, inter 17 animales supervivente 2 a 29 dies post acute occlusion coronari, 13 (77 pro cento) monstrava un abundante circulation collateral.

Iste studios prova que un significative circulation collateral intercoronari pote disveloppar se intra 2 dies post acute ligation coronari.

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A great discovery is not a terminus, but an avenue leading to regions hitherto unknown. We climb to the top of the peak and find that it reveals to us another higher than any we have yet seen, and so it goes on.—GEORGE THOMSON. *Centenary of J. J. Thomson.* Science **124:** 1195, 1956.

Dissecting Aneurysm of the Aorta Secondary to Tuberculous Aortitis

By JOHN J. MEEHAN, M.D., BERNARD H. PASTOR, M.D., AND ANTHONY V. TORRE, M.D.

TUBERCULOUS aortitis is rare, only 29 cases having previously been reported. All but 1 of these have been associated with aneurysm, but in none has dissection been present. We believe the following to be the first reported case of dissecting aneurysm secondary to tuberculous aortitis.

CASE REPORT

G. P., a 55-year-old man was admitted to the hospital on March 28, 1953, with abdominal pain of 1 week's duration, cough, and dyspnea. The pain radiated to the chest, back, and interscapular region. There was a history of genitourinary and skeletal tuberculosis dating back to 1919, and the left epididymis and left kidney had been removed. Hypertension had been present for 6 or 7 years. Since April 1952 he had been treated for recurrent tachycardia and syncope. The past history was otherwise not significant, and the family history was negative.

On physical examination, the blood pressure was 230/130, the heart was enlarged, and there were signs of mild congestive heart failure. Grade III hypertensive retinopathy and optic atrophy of the right eye were present.

There was a normal hemogram, the blood urea nitrogen was normal, and the serologic test for syphilis was negative. An electrocardiogram showed left ventricular hypertrophy and digitalis effect.

Roentgenologic examination of the chest revealed cardiac enlargement, chiefly left ventricular, a tortuous elongated aorta, and old healed calcific tuberculosis in both upper lobes (fig. 1). An intravenous urogram disclosed a normal right pelvocalyceal system and ureter; the left was not visualized. X-rays of the spine revealed evidence of both healed and active tuberculosis involving the first 4 lumbar vertebrae.

Several days after admission hoarseness developed, and prominence of the left hilum was seen in the chest films (fig. 1*A*). Planigraphic examination of the left hilum demonstrated that the enlargement was due to vascular shadows and not to a tumor mass. Bronchoscopy showed that the hoarseness was due to paralysis of the left vocal cord, but no endobronchial lesion was seen. There was some decreased mobility of the left main bronchus. Chest fluoroscopy on April 22, approximately 3 weeks after admission, revealed deviation of the esophagus to the left and narrowing of its lower 4 centimeters. One week later paralysis of the left leaf of the diaphragm was noted. The esophageal changes were thought to represent esophagitis rather than neoplasm from the roentgenologic standpoint. On May 11, the left leaf of the diaphragm was still paralyzed (fig. 2). Tortuosity of the aorta was again observed but it was not noted that an increase in size and irregularity had occurred.

Diagnoses of hypertensive cardiovascular disease and healed pulmonary and bone tuberculosis were made. The cause of the esophageal abnormality and the paralysis of the vocal cord and diaphragm was not determined during this hospital admission.

The patient was readmitted to the hospital in November 1953 in congestive heart failure. Roentgenograms at this time showed an increase in the width of the aortic knob and increased width and tortuosity of the descending aorta (fig. 3). The left leaf of the diaphragm had returned to its normal position and its excursion was normal. There was marked distortion of the esophagus due to extrinsic pressure. A diagnosis of dissecting aneurysm of the aorta was made. The previously unexplained vocal cord and phrenic paralysis was attributed to pressure on the phrenic and recurrent laryngeal nerves by the aneurysm.

The patient was again hospitalized in July 1955 for congestive heart failure. The blood pressure was 210/150. Except for an apparent increase in heart size, there were no significant differences from the previous physical findings. Roentgenograms of the chest revealed further increase in the width of the thoracic aorta.

The patient was admitted for the last time in September 1955 in acute congestive heart failure. There was no chest pain. Despite therapy, he died 1 hour later.

At autopsy there was a dissecting aortic aneurysm extending from just beyond the origin of the left subclavian artery to a level just above the origin of the renal arteries. The proximal portion was saccu-

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Presented at the Regional Meeting of the American College of Physicians, Philadelphia, Pa., January 18, 1957.

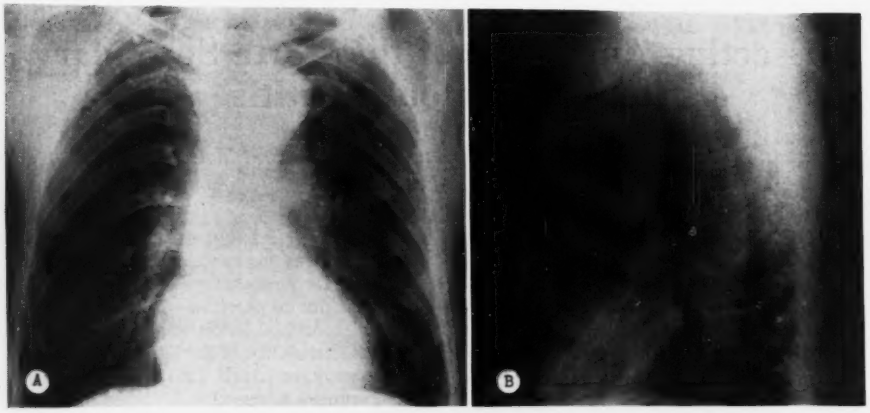

FIG. 1. Initial roentgenogram of the chest showing cardiac enlargement, tortuous elongated aorta, and old healed calcific tuberculosis in both upper lobes. *A*. Posteroanterior projection. *B*. Left lateral projection.

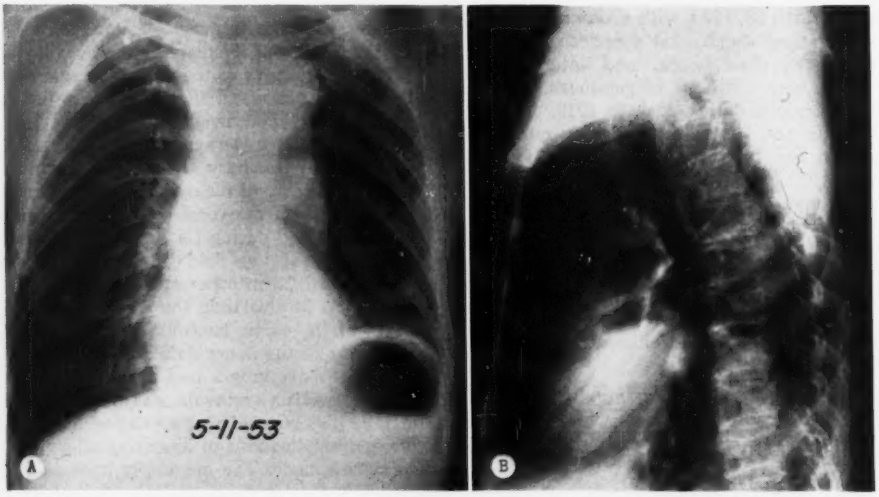

FIG. 2. Chest roentgenogram showing increased width of aorta and paralysis of left leaf of diaphragm. *A*. Posteroanterior projection. *B*. Left lateral projection.

lar, measuring 6.5 by 6 by 3 cm.; the distal portion was cylindrical, 17 cm. in length (fig. 4*A*). The celiac and superior mesenteric arteries were not involved in the process, but both common iliac arteries were markedly dilated and had aneurysmal bulges containing mural thrombi. In the opened, dissected segment communication with the true aortic lumen could be seen at the junction of the saccular and cylindrical portions. At the distal end of the dissection, recommunication with the true aortic lumen had occurred (fig. 4*B*). Within the false lumen were several organizing thrombi. Marked atherosclerosis, with numerous areas of ulceration, was present throughout the aorta.

Microscopic examination of the aortic wall revealed 2 distinct processes: severe ulcerative atherosclerosis, and caseating granulomatous involvement of the adventitia (fig. 5*A*). In areas not involved by dissection there was abnormal intima of varying thickness, but the fibroelastic media was intact, and the adventitia was normal. Toward the area of dissection there was gradual transition in the adventitia to a longitudinally oriented mass of caseating granulomatous tissue. It was in this layer that dissection had taken place, so that the false lumen was lined by caseation tissue. At the proximal and distal ends of the dissection, the granuloma had extended into and destroyed the fibroelastic media. At these 2 points communication between the true and false aortic lumen had taken place through an intimal tear. The granuloma was consistent in appearance with tuberculosis (fig. 5*B*), and acid fast

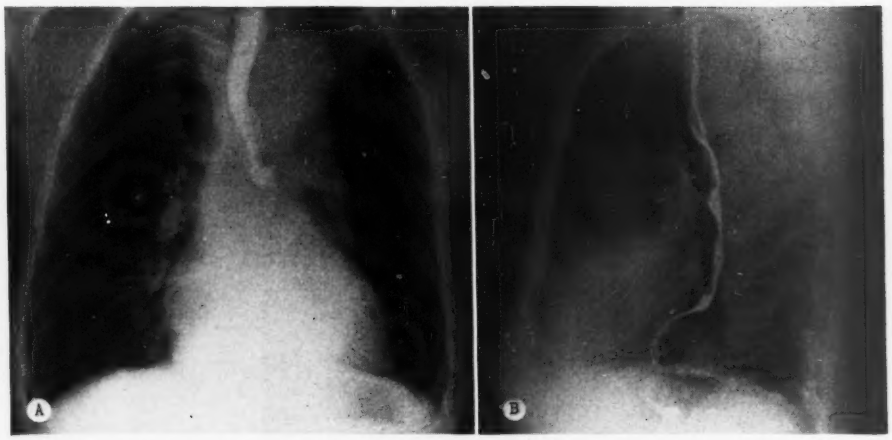

FIG. 3. Chest roentgenogram showing further increase in width and tortuosity of aorta and marked distortion of esophagus by extrinsic pressure. Diaphragm has returned to normal level. *A*. Posteroanterior projection. *B*. Lateral projection.

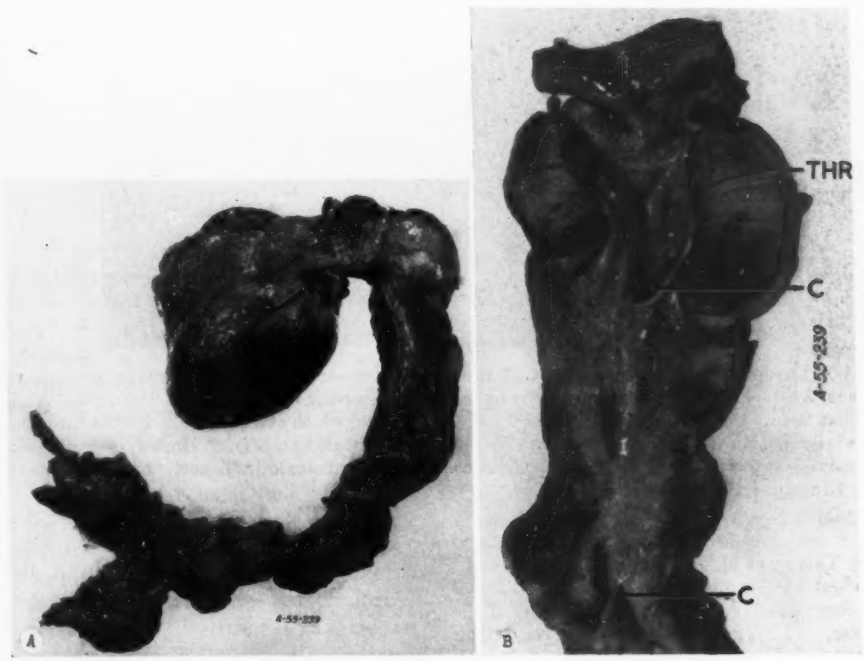

FIG. 4. *A*. Autopsy specimen showing extensive involvement of aorta by dissecting aneurysm. *B*. Dissected segment open showing points of communication between true and false aortic lumen (*C*) and large laminated thrombus in saccular portion (*Thr*).

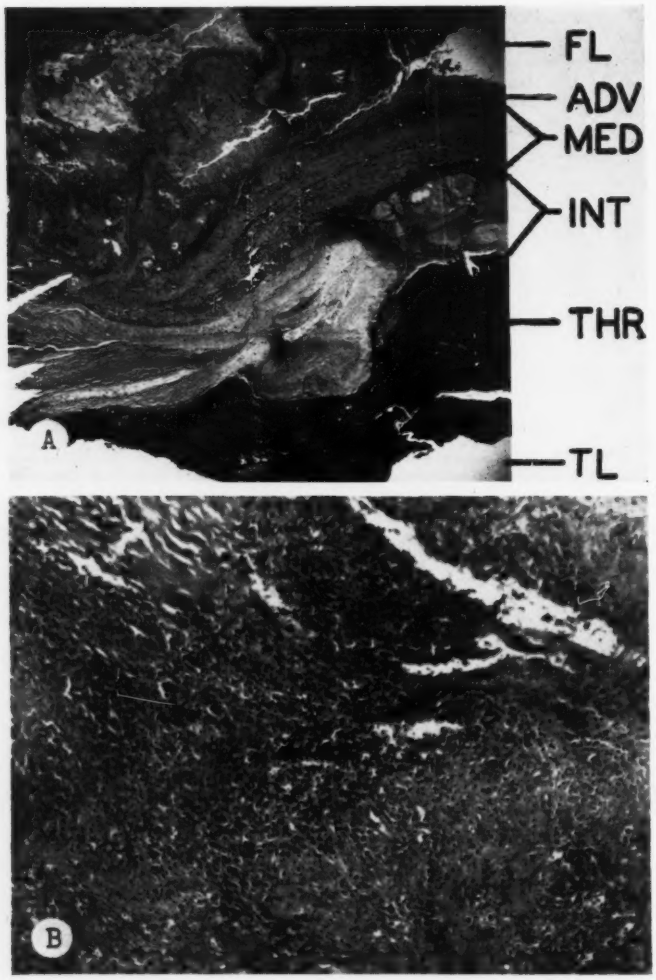

FIG. 5. *A*. Low-power photomicrograph (× 12) showing involvement of adventitia (*Adv*) by caseating granulomatous tissue. At upper right, adventitia is split by lumen of dissecting aneurysm (*Fl*). The media (*Med*) is intact at right but toward the left becomes involved by the granuloma, which extends to and breaks through the atheromatous intimal layer (*Int*). Large thrombus (*Thr*) lines true aortic lumen (*Tl*). *B*. Higher power photomicrograph (× 65) showing granuloma with many giant cells consistent with tuberculosis. Tubercle bacilli were demonstrated in other Kinyoun-stained sections.

bacilli were demonstrated in Kinyoun-stained sections. There was diffuse tuberculous involvement of the chest wall, lumbar vertebrae, lungs, adrenal glands, liver, spleen, prostate, and the stump of the left ureter, but no involvement of periaortic lymph nodes was found.

DISCUSSION

Tuberculosis of the smaller blood vessels, either by local extension or as part of a diffuse miliary process, is not uncommon. Tuberculous involvement of the large vessels, however, particularly the aorta, is rare. Only 29 cases of tuberculous aortitis have previously been reported. Twenty-one of these were included in a review by Gellerstedt and Säfwenber[1] in 1933 and since then 8 additional cases have been reported.[2-9] All the other cases except that of Waser[3] have been associated with aneurysm,

but ours is the first in which dissection of the aorta has been present. The aorta was most frequently involved by contiguity, usually by spread from adjacent lymph nodes. In 5 cases, including the present one, the infection was apparently blood borne.

A specific etiology for aortic dissection is rarely recognized[10, 11] and the majority of dissections are classified as "idiopathic." Dissecting aneurysm, as it presents itself clinically, probably results from 2 distinct processes. Splitting of the aortic wall is usually attributed to disease of the media, so-called medionecrosis cystica, and rupture of diseased medial nutrient vessels is believed to be responsible for the formation of a hematoma within the dissected segment. Atherosclerotic degeneration of the intima then permits an intimal tear, with resulting communication between the dissection and the aortic lumen. The present case differs in that the dissection occurred in the adventitia instead of the media. The adventitia was widely involved by a specific granulomatous process and at only 2 points did the necrosis extend to involve the media. Here the process merged with the atheromatous intima and the intimal tear occurred, establishing communication with the aortic lumen.

Whether aortic dissection is of known etiology or "idiopathic," certain predisposing factors are recognized. These are coarctation and other anomalies of the aorta, pregnancy, Marfan's syndrome, and hypertension. Hypertension is nearly always present at the time of dissection. Even in those patients whose blood pressure is not elevated, some evidence of hypertensive vascular disease is usually found either in the history, the physical findings, or the findings at autopsy. In some cases, however, the hypertension may be the result of the dissecting aneurysm rather than a predisposing cause, by a mechanism similar to that in coarctation of the aorta, with proximal hypertension and distal hypotension.

The clinical picture of dissecting aneurysm has been described elsewhere[12-16] and will not be discussed in detail here. Several features, however, deserve re-emphasis. The presenting complaint most frequently encountered is severe pain in the chest or abdomen, radiating often to the back, the interscapular region, the neck, and the legs. Although this patient's initial pain had the characteristic distribution it was mild and did not persist. It should be recognized that dissection may be gradual, and the classical acute or subacute clinical picture of pain, shock, collapse, and death in a matter of hours or days may not be present. Extensive dissection has been observed at autopsy from the aortic arch to the bifurcation of the aorta without any history of symptoms referable to the lesion.

Of particular clinical interest in the present case was the occurrence of hoarseness due to involvement of the recurrent laryngeal nerve, which has previously been reported, and the transient phrenic paralysis to which we can find no previous reference.

The present case is an example of so-called "healed" dissecting aneurysm, resulting from distal re-entry from the dissection into the true aortic lumen. This is reported to occur in approximately 25 per cent of aortic dissections.[13] The patient may die later as a result of rupture of the aneurysm but more commonly death results from some other related or unrelated cause. Recent attempts at surgical therapy of dissecting aneurysm have been patterned after this natural "healing." They have been directed at re-establishment of aortic flow by the production of a fenestration between the dissection and the true aortic lumen.[17-19] The ultimate success of this approach remains to be demonstrated.

Summary

Tuberculous aortitis is rare, only 29 cases having previously been reported. The first known case of dissecting aneurysm of the aorta secondary to tuberculous aortitis is described. The site of dissection was in the adventitia instead of the usual location in the media. The possibility of gradual aortic dissection without the classical acute picture is emphasized.

Summario in Interlingua

Aortitis tuberculotic es rar. Solmente 29 previe casos se trova in le litteratura. Es hic describite le prime cognoscite caso de aneurysmo dissecante del aorta, occurrente secundari

a aortitis tuberculotic. Le sito del dissection esseva le adventitia in loco del usual sito in le media. Es signalate le possibilitate de un dissection aortic gradual sin le acute tableau classic.

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Other schools have earned a reputation in physiology and comparative anatomy, and those branches of medicine which are termed theoretic; but the enduring fame of the Dublin contributions to science arises from their essential practicality and truthfulness. They are records of unbiassed observation made by men originally well educated, and brought up in a practical school.—William Stokes His Life and Work (1804–1878) by his son WILLIAM STOKES. London, T. Fisher Unwin, MDCCCXCVIII, p. 162.

Pathophysiology of Rheumatic Fever

Alterations in the Na^{24} Space and in the Exchangeable Sodium and Potassium Contents

By JERRY K. AIKAWA, M.D.

Radioisotopic technics were used to explore physiologic aberrations that may characterize individuals with acute rheumatic fever. No significant changes were noted in serial measurements of the blood volume or serum sodium and potassium concentrations. Most of the individuals with severe disease showed an initial value for radiosodium space of more than 330 ml./Kg. of body weight, with no evidence of edema. The exchangeable sodium content of the body correlated well with the radiosodium space. These changes are difficult to explain solely on the basis of extracellular edema, and are interpreted as suggesting that the intracellular content of sodium or that in bone is increased during acute rheumatic fever. An intracellular increase in sodium may be due to an alteration in the permeability of cell membrane induced by an immune mechanism.

AT THE present time there is much evidence to support the hypothesis that rheumatic fever is a consequence of a hypersensitivity reaction to an antigen or antigens produced by a previous infection with a beta hemolytic streptococcus.[1] Although extensive epidemiologic and bacteriologic studies on the pathogenesis of rheumatic fever have been made, little work has been done on the nature of the abnormal physiologic processes occurring during the acute disease state. Data presented in a previous preliminary note suggested that acute rheumatic fever may be associated with an alteration in the permeability of cell membranes.[2] Such a hypothesis is compatible with the known effects of experimental in vivo antigen-antibody reactions on the distribution of body fluids and electrolytes.[1]

The purpose of the present study was to make further physiologic measurements in rheumatic subjects, following the alterations in the distribution of electrolytes by means of radioactive isotopes of sodium and potassium.

MATERIAL AND METHODS

Subjects. Twenty patients, 14 males and 6 females, with the diagnosis of acute or chronic active rheumatic fever were studied. Their ages ranged from 5 to 41 years, and 16 patients were under 17 years of age. The diagnosis was made on the basis of the history and the physical signs, according to the diagnostic criteria of Jones.[3] The cases were divided into 3 categories according to the clinical severity of the disease, and these groups were further subdivided according to the type of treatment given (table 1). *Group 1:* Eleven patients had clinical and laboratory evidences of carditis, with persistence of rheumatic activity for longer than a month after the onset of symptoms; these 11 cases were classified as severe (3+). *Group 2:* Four patients who had evidences of carditis recovered within a month after the onset of the rheumatic process, and their cases were classified as moderately severe (2+). *Group 3:* Five patients had rheumatic fever with no evidence of carditis, and responded very promptly to hospitalization and therapy; these cases were considered mild (1+).

The general plan of therapy was to administer acetylsalicylic acid, sodium salicylate, aminopyrine, cortisone, or ACTH until the clinical and laboratory evidences of rheumatic activity had subsided. The dosage of the drug was then gradually reduced. If signs of rheumatic activity recurred, an intermediate dosage was continued until all signs of rheumatic activity had again subsided.

All subjects were given a regular hospital diet containing a maximum of 3 to 4 Gm. of sodium daily.

Isotopes. Isotopic sodium (Na^{24}) and potassium (K^{24})* were prepared for injection in the manner previously described.[4, 5]

Measurement of Radioactivity. Early in the study, the activity of the urine and serum specimens was

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Dr. Aikawa is an Established Investigator of the American Heart Association.

This study was aided in part by a grant-in-aid from the American Heart Association and in part under a contract with the U. S. Atomic Energy Commission.

* K^{42} and Na^{24} were supplied by the Oak Ridge National Laboratory, Oak Ridge, Tennessee, on allocation from the U. S. Atomic Energy Commission.

TABLE 1.—*Classification of Cases*

Clinical severity	Therapy				Total Cases
	Salicylates	Aminopyrine	ACTH	Cortisone	
3+ (Group 1)	2, 3, 9, 11*	6, 7	10, 12, 17	8, 19	11
2+ (Group 2)	1, 4, 5			18	4
1+ (Group 3)	13, 14, 15, 16			20	5
Total cases	11	2	3	4	20

* The figure indicates the case number in the text, tables, and figure 1.

determined with a dipping Geiger-Müller tube and a scaling circuit. Recent measurements have been made with a well-type scintillation counter. A total of 10,000 counts were made on each sample. All determinations were corrected for physical decay.

Determination of Serum Sodium and Potassium. The sodium and potassium concentrations in the serum or urine were determined early in the course of the study with a Beckman flame photometer by the direct method, and recently with a Baird flame photometer, by the lithium internal standard method.

Procedure

Determination of Exchangeable Sodium Content (Na_e). Each subject received from a calibrated syringe 1.5 μc. Na^{24} per Kg. of body weight, contained in a sterile 0.9 per cent solution of sodium chloride. All urine voided for the next 24 hours was collected, and the Na^{24} content of the pooled specimen was determined. Blood specimens were obtained at 3 and 24 hours after the injection of Na^{24}, and the specific activity of sodium in the serum was determined. The following formula was used to calculate the value for the exchangeable sodium content of the body:

$$Na_{-e} = \frac{Na_{-i}^{24} - Na_{-u}^{24}}{Na_{-s}^{24}/Na_{-s}^{23}}$$

Na_{-e} = quantity of exchangeable sodium in milliequivalents (mEq.).

Na_{-i}^{24} = quantity of radiosodium administered.

Na_{-u}^{24} = quantity of radiosodium excreted in the pooled specimen of urine.

Na_{-s}^{24} = concentration of radiosodium in the serum at 24 hours.

Na_{-s}^{23} = concentration of nonradioactive sodium in the serum at 24 hours.

$Na_{-s}^{24}/Na_{-s}^{23}$ = specific activity of the serum at 24 hours.

Preliminary studies in this laboratory revealed that the Na_e measurement was reproducible within 5 per cent in edema-free, hospitalized subjects with various chronic diseases whose condition was stabilized.

Radiosodium Space. The volume of dilution of the injected Na^{24} at 3 hours was calculated as follows:

$$Na^{24} \text{ space in liters} = \frac{\text{total } Na^{24} \text{ activity injected}}{\text{serum } Na^{24} \text{ concentration per liter at 3 hours}}.$$

The exchangeable potassium content was determined in a manner similar to the determination of the exchangeable sodium content and has been previously described.[4, 5]

Determination of Blood Volume. The plasma volume was determined by the T-1824 dye (Evans blue) method.[6] The hematocrit value was determined on venous blood collected without stasis in bottles containing potassium and ammonium oxalate; the Wintrobe hematocrit tubes were centrifuged for 30 minutes at 3,000 revolutions per minute. The total blood volume was calculated from the hematocrit reading and the plasma volume.

RESULTS

Radiosodium (Na^{24}) Space

Serial measurements of the radiosodium space were available in 17 patients (table 2, fig. 1). The upper range of normal for this value is considered to be 330 ml./Kg.[4]

Group 1. Serial Na^{24} space determinations were made in 10 of these cases (fig. 1). In 5 patients (cases 2, 7, 9, 11, and 12) the initial determination was obtained within 10 days after the onset of symptoms; with 1 exception (case 7) all initial values were greater than 330 ml./Kg., the highest value being 528 ml./Kg. (case 6). In the remaining 5 patients (cases 3, 6, 8, 10, and 17) the initial measurement was made between 20 and 62 days of the onset of the disease, and all values were above 330 ml./Kg. Thus, in only 1 instance (case 7) was the initial value for Na^{24} space lower than 330 ml./Kg. None of these 10 individuals had clinically demonstrable edema at any time during the period of observation. In

TABLE 2.—*Changes in the Radiosodium Space, Exchangeable Sodium Content, and Serum Electrolytes During Rheumatic Fever Therapy*

Case	Age	Sex	Severity	Days after onset	Wt. (Kg.)	Na^{24} Space (ml./Kg.)	Na_e (mEq./Kg.)	Serum electrolytes (mEq./L.)		ESR (mm./hr.)	Therapy
								Sodium	Potassium		
1	16	M	2+	4	51.1	368		122	4.1	34	ASA, 3.6 Gm daily, days 4–23
				10	50.2	419		133	4.0	41	
				17	49.8	388		115	4.5	13	
				24	52.1	337		145	4.4	9	
				35	55.9	319		132	4.1	10	
				70	51.9	316		—	—	0	
2	15	M	3+	4	44.1	463		124	3.6	38	ASA, 3.6 Gm. daily, days 4–25, 33–46
				11	44.5	458		129	3.5	34	
				18	44.3	325		137	4.1	26	
				32	46.4	366		129	3.8	17	
				39	45.9	327		143	4.2	15	
				54	50.0	292		129	3.8	8	
				82	52.4	233		—	—	5	
3	17	M	3+	21	53.0	543		140	3.9	23	ASA, 3.6 Gm. daily, days 23–34
				27	50.9	348		121	3.8	21	
				34	50.7	371		130	4.2	15	
4	41	M	2+	7	71.8	275	41	140	5.0	18	ASA, 2.4 Gm daily, days 7–20
				15	71.1	250	41	135	5.4	3	
				21	70.5	245	44	145	5.8	8	
5	13	F	2+	11	49.1	268	41	143	5.0	28	ASA, 2.4 Gm. daily, days 13–19
				17	47.7	239	42	154	5.1	13	
6	14	M	3+	16	35.5	400	60	134	—	30	Aminopyrine, 0.9–1.8 Gm. daily, days 16–34
				23	40.5	380		143	3.9	28	
				30	40.0	350	52	142	3.9	18	
				37	40.5	318	48	147	3.9	24	
7	26	F	3+	8	51.6	271	58	149	—	32	Aminopyrine, 1.2 Gm. daily, days 9–18; ASA, 3–6 Gm. daily, days 19–44
				15	51.9	319	51	141	5.6	38	
				22	52.7	301	51	148	5.8	38	
				29	52.7	258	45	147	3.8	40	
				36	52.3	299	49	147	4.5	40	
8	13	M	3+	62	45.5	331	48	142	4.4	11	ASA, 2.4 Gm. daily, days 69–77. Cortisone, 200 mg. daily, days 79–97
				70	44.5	311	48	139	3.9	39	
				76	43.6	332	55	145	4.4	32	
				83	43.2	291	55	149	4.8	32	
9	9	F	3+	8	26.9	500	49	142	–	49	ASA, 2.0 Gm. daily, days 2–44
				15	26.3	320	47	138	—	23	
				22	27.3	320	48	142	—	31	
				36	27.6	300	42	135	—	23	
				48	28.2	300	43	136	—	11	
				57	27.9	300	46	138	—	10	
				246	30.9	280	40	135	5.0	6	

TABLE 2.—*Continued*

Case	Age	Sex	Severity	Days after onset	Wt. (Kg.)	Na^{24} Space (ml./Kg.)	Na_e (mEq./Kg.)	Serum Electrolytes (mEq./L.)		ESR (mm./hr.)	Therapy
								Sodium	Potassium		
10	11	M	3+	20	32.0	377	64	148	3.1	0	ACTH gel, 65 units daily, days 16–66
				48	34.3	274	47	152	3.1	1	
				62	38.2	284	38	145	4.4	1	
				77	37.0	—	39	141	4.4	3	
11	5	M	3+	6	17.3	528	59	136	—	46	ASA, 1 Gm. daily, days 7–50
				13	16.9	345	63	138	—	—	
				20	17.3	348	54	142	—	16	
				34	17.5	319	47	138	—	14	
				48	17.8	302	45	136	—	4	
				62	17.7	308	47	134	—	—	
				243	18.5	328	54	143	4.4	—	
12	8	F	3+	7	18.2	378	59	138	4.0	50	ASA, 0.5 Gm. daily, days 2–8; ACTH gel, 50 units daily, days 5–30
				15	18.6	327	53	140	3.8	6	
				27	18.6	326	53	148	3.9	1	
13	7	F	1+	10	31.0	259	38	135	—	28	ASA, 3 Gm. daily days 12–41
				16	32.0	250	37	134	—	25	
				31	30.4	254	40	138	—	9	
14	14	M	1+	7	52.0	311	47	135	—	37	ASA, 4.2 Gm daily, days 4–49
				14	52.7	323	46	138	4.2	34	
				21	52.0	309	48	140	4.0	33	
				35	55.2	303	48	141	3.7	12	
				50	56.8	293	46	141	3.7	7	
15	28	F	1+	23	62.3	215	34	137	3.9	48	ASA, 8 Gm. daily, days 15–34, 47–59
				38	61.1	214	35	141	3.9	28	
				52	62.3	215	35	145	3.8	40	
16	15	M	1+	8	59.5	328	48	138	—	32	ASA, 4 Gm. daily, days 3–34
				15	58.9	302	47	141	—	7	
				22	60.7	306	49	139	—	14	
				29	61.5	303	43	138	—	8	
				36	62.4	292	44	139	—	8	
17	14	M	3+	61	35.1	372	54	137	4.0	0	ACTH gel, 80 units daily, days 59–90
				68	35.9	322	51	138	4.1	0	
				75	36.2	300	49	140	4.0	0	

ESR = erythrocyte sedimentation rate.
ASA = acetylsalicylic acid or sodium salicylate.

all instances except 2 (cases 7 and 8), subsequent values were at least 50 ml./Kg. lower than the initial values, the maximum decrease being 230 ml./Kg. (case 2).

Eight of the 10 patients in this group gained weight (0.4 to 8.3 Kg.) at a time when the absolute value for the Na^{24} space was decreasing. Two patients (cases 3 and 8) lost weight. In one (case 3) the Na^{24} space decreased 11 liters as the body weight decreased 2.3 Kg.; in the other subject (case 8) the Na^{24} space dropped 2.5 liters as the body weight decreased 2.3 Kg.

Group 2. Initial Na^{24} space determinations were made between 4 and 11 days of the onset of the disease, and were below 330 ml./Kg. in 2 patients (cases 4 and 5) and above this value in 1 (case 1). In only 1 instance (case 1) did

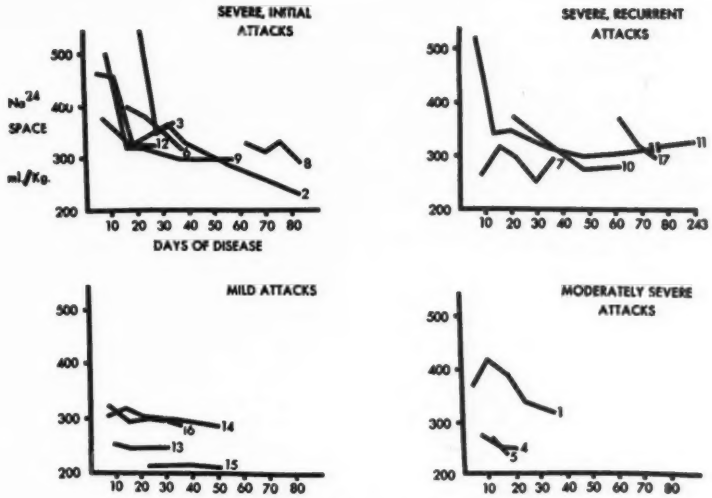

FIG. 1. Radiosodium space in rheumatic fever

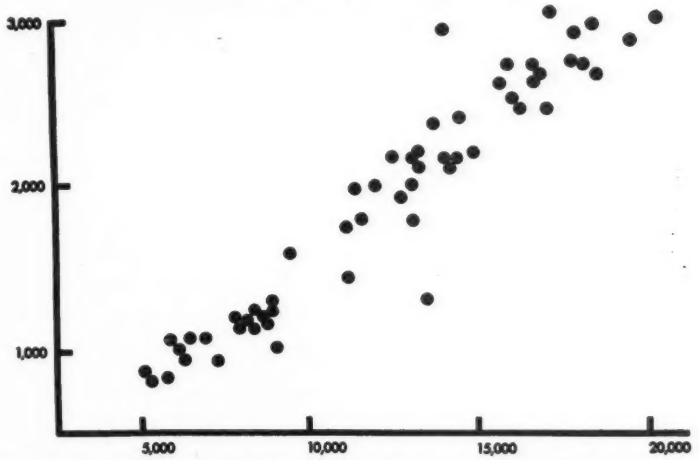

FIG. 2. Correlation of changes in Na_e (*ordinate*, mEq.) with those in Na^{24} space (*abscissa*, ml.).

the Na^{24} space/Kg. subsequently decrease more than 50 ml./Kg. None of the patients had clinical edema.

One subject (case 1) gained 4.8 Kg. and the other 2 (cases 4 and 5) lost 1.3 and 1.4 Kg. in body weight; the Na^{24} space decreased between 2 and 3 L. during this time.

Group 3. Initial Na^{24} space values obtained in 4 patients between 7 and 23 days of onset ranged between 215 and 328 ml./Kg. In none of these patients did subsequent values decrease more than 50 ml./Kg. None of these 5 patients showed clinical edema.

Four of the 5 subjects in this group gained weight (0.9 to 4.8 Kg.) during the period of study, and 1 (case 15) lost 1.2 Kg. No striking changes in the Na^{24} space were noted in any of these subjects.

Exchangeable Sodium Content (Na_e)

Serial measurements of the exchangeable sodium content were available in 14 patients (table 2). The upper range of normal for this value is considered to be 46.0 mEq./Kg.[7]

Group 1. Serial Na_e measurements were available in 8 patients in this category (cases 6–12, and 17). All initial values were higher than 46.0 mEq./Kg. (range, 48.0 to 64.0

TABLE 3.—*Changes in the Exchangeable Potassium Content and Serum Electrolytes During Rheumatic Fever Therapy*

Case	Age	Sex	Severity	Days after onset	Wt. (Kg.)	K_e (mEq./Kg.)	Serum electrolytes (mEq./L.)		ESR (mm./Hr.)	Therapy
							Sodium	Potassium		
4	41	M	2+	15	71.1	41	135	5.4	3	ASA, 2.4 Gm. daily, days 7–20
				21	70.5	36	145	5.8	8	
8	13	M	3+	62	45.5	41	142	4.4	11	ASA, 2.4 Gm. daily, days 69–77.
				70	44.5	46	139	3.9	39	Cortisone, 200 mg. daily, days
				76	43.6	38	145	4.4	32	79–97
				83	43.2	39	149	4.8	32	
18	25	M	2+	12	89.5	27	139	4.7	31	ASA, 7 Gm. daily, days 11–22;
				27	87.6	32	149	4.8	8	ASA, 5 Gm. daily + cortisone,
				41	87.3	40	149	4.3	13	300 mg. daily, days 23–40
19	6	M	3+	6	20.1	39	150	4.5	34	Cortisone, 135 mg. daily, days
				48	26.7	43	149	4.3	3	3–60
				62	28.3	43	152	4.6	2	
20	11	M	1+	13	28.5	46	149	5.6	8	Cortisone, 100 mg. daily, days
				27	29.4	43	136	4.6	0	4–42

ESR = erythrocyte sedimentation rate.
ASA = acetylsalicylic acid or sodium salicylate.

mEq./Kg.), even though edema was not clinically evident. In 7 of the 8 patients (exception, case 8) the Na_e/Kg. subsequently decreased more than 5 mEq./Kg. (range, −5 to −26 mEq./Kg.). In 4 of the cases, the lowest value obtained remained higher than 46.0 mEq./Kg.

Group 2. Serial Na_e values were obtained in cases 4 and 5. In both cases the initial values for Na_e/Kg. were 41.0 mEq./Kg. and were not significantly altered during the period of observation.

Group 3. Serial Na_e values were obtained in cases 13–16. Two of the 4 initial values were slightly higher than 46.0 mEq./Kg. (47 and 48 mEq./Kg. respectively in cases 15 and 16). In case 16, a decrease of 5 mEq./Kg. subsequently occurred. The other 3 patients showed no significant changes in this value.

There was excellent correlation between the values for the Na^{24} space and the exchangeable sodium content (fig. 2).

Exchangeable Potassium Content (K_e).

The reported range for K_e in normal men is 35.6–55.6 mEq./Kg., the mean being 46.3 mEq./Kg. (table 3).[5] For normal women the range in one series[8] was 25.1–35.0 mEq./Kg., with a mean of 31.5 mEq./Kg.; in another series[7] it was 28.6–47.2 mEq./Kg., with a mean of 40.7 mEq./Kg. Data of a similar nature for normal children are not yet available.

Group 1. Serial K_e determinations in a patient (case 19) with severe acute rheumatic fever rose from a low normal of 780 mEq. (39 mEq./Kg.) on the sixth day to 1208 mEq. (43 mEq./Kg.) as the subject gained 8 Kg. in weight while receiving large doses of cortisone. One patient (case 8) with chronic active rheumatic fever, in whom serial Na_e as well as K_e determinations were performed, showed normal initial K_e values which first increased approximately 200 mEq., and subsequently decreased to about 200 mEq. below the initial value. In this subject a reciprocal relationship between the Na_e and the K_e was suggested, since the value for Na_e/Kg. increased as that for K_e/wt. decreased, and the sum of the K_e and the Na_e remained fairly constant at all times.

Group 2. K_e measurements were available in 2 subjects with moderately severe rheumatic

TABLE 4.—*Changes in the Plasma Volume, Hematocrit, and Total Blood Volume during Rheumatic Fever Therapy*

Case	Days after onset	Wt. (Kg.)	Plasma volume (ml./Kg.)	Hematocrit (vol. %)	Total blood volume (ml./Kg.)
1	4	51.1	58	37.3	93
	10	50.2	67	35.9	104
	17	49.8	45	39.3	75
	24	52.1	—	39.4	—
	35	55.9	57	39.1	94
	70	51.9	56	39.7	93
2	4	44.1	66	39.1	108
	11	44.5	58	40.2	97
	18	44.3	69	40.8	117
	32	46.4	44	43.1	77
	39	45.9	41	42.1	71
	54	50.0	57	42.9	99
	82	52.4	59	42.2	103
3	21	53.0	70	37.3	112
	27	50.9	80	38.5	131
	34	50.7	57	41.0	97
4	7	71.8	39	45.7	72
	15	71.1	50	49.5	83
	21	70.5	49	48.7	94
5	11	49.1	51	34.3	77
	17	47.7	53	35.7	83
6	16	35.5	86	33.0	129
	23	40.5	60	34.0	91
	30	40.0	63	35.0	98
	37	40.5	58	38.2	94
7	8	51.6	55	37.4	88
	15	51.9	57	34.5	86
	22	52.7	52	36.1	82
	29	52.7	60	31.4	88
	36	52.3	58	36.6	92
8	62	45.5	57	39.4	94
	70	44.5	53	39.8	89
	76	43.6	62	38.4	101
	83	43.2	57	40.1	95

fever (cases 4 and 18). In case 18 the initial value for K_e/wt., obtained 12 days after onset of the disease, was subnormal and increased progressively to a value of 40 mEq./Kg. as the rheumatic process subsided by 41 days; this increase occurred while the patient was receiving cortisone and supplemental potassium chloride. In the other patient, who was treated with salicylates, K_e decreased by 360 mEq. between 15 and 21 days after onset, but remained within the normal range.

Group 3. Two K_e determinations were made in 1 patient (case 20) with a mild disease; both values were within the normal range.

Other Values. A serum potassium value of less than 3.5 mEq./L. was found in only 1 patient (case 10), who was receiving ACTH gel at the time of this determination (table 4). A potassium value higher than 5.5 mEq./L. was obtained in 3 subjects (cases 4, 8, and 20).

A serum sodium concentration of less than 134 mEq./L. was found in 3 patients (cases 1, 2, and 3), and a value higher than 150 mEq./L. was obtained in 3 patients (cases 5, 10, and 19). There was no correlation between the changes in the serum sodium concentration and the exchangeable sodium content or the radiosodium space.

The plasma volume changes showed no consistent trend during the course of therapy. In 6 of the 7 patients (cases 1–6) in whom serial hematocrit determinations were made early in the course of the disease, the values increased as clinical improvement occurred. In 1 patient (case 7) it decreased before rising. The total blood volume showed no consistent trends during therapy.

DISCUSSION

Factors Influencing the Radiosodium Space. The value for the radiosodium space, as determined by the method used, may be influenced by several factors:

Interstitial Edema. Previous studies[4] have shown that values for Na^{24} space greater than 330 ml./Kg. are usually associated with clinical pitting edema—as, for example, in congestive heart failure. The increased Na^{24} space in rheumatic fever cannot be explained on this basis alone, since values in excess of 500 ml./Kg. were found in the absence of any pitting edema. Furthermore, if the increased Na^{24} space were due primarily to extracellular fluid retention, loss of this fluid by diuresis should result in a more or less parallel decline in body weight. In most of the rheumatic subjects the body weight increased during therapy as the Na^{24} space decreased, and diuresis did not occur. It

is difficult, therefore, to account for the abnormally high values for Na^{24} space solely on the basis of interstitial edema.

Intercellular Cement Substance. The rate of diffusion of an ion into the extravascular space following intravascular injection may be influenced by the nature and the state of the intercellular cement substance—the hyaluronic acid and chondroitin sulfuric acid systems. The radiosodium space is increased, for instance, in myxedema, where the excess of colloidal substances in the interstitium causes abnormal retention of salt and water. Such an abnormal physiologic process is manifested clinically by puffiness and generalized nonpitting edema, and thyroid therapy results in loss of body weight and a parallel decrease in the radiosodium space.[9]

The apparent increase in the 3-hour value for the Na^{24} space in rheumatic subjects may be explained by an increase in the rate of exchange between the injected radioactive atoms and the native ions in the intercellular cement system. That connective tissue changes occur in acute rheumatic fever has been established. Were this the only factor responsible for the apparent increase in Na^{24} space, however, the 24-hour value for exchangeable sodium content would not necessarily be elevated. The finding in the present study of a remarkable correlation between the Na^{24} space and the exchangeable sodium content suggests that the body's store of sodium is indeed increased during acute rheumatic processes; this excess sodium, however, does not appear to be extracellular in an amount sufficient to induce clinical pitting edema.

Bone Sodium. If the excess exchangeable sodium is not extracellular, there is a possibility that it might be adsorbed on bone in excessive amounts or exchanged with bone sodium at an increased rate. The nature and regulation of bone sodium are poorly understood, and it is conceivable that an increase in the exchangeable sodium content or the radiosodium space might be due to an abnormality in exchange or storage in bone. However, such a possibility is not thought to be as likely as the following explanation.

Tissue Cell Membrane. The data best fit the hypothesis that, in acute or chronic active rheumatic fever, the normal relative impermeability of the tissue cell membrane to the sodium ion is altered, with a resultant increase in the rate of exchange of sodium between the extracellular and intracellular compartments and in the amount of sodium within cells. Thus, the radiosodium space and the exchangeable sodium content are increased to an extent which is out of proportion to the amount of clinical edema present.

This increase in the intracellular store of sodium appears to be accompanied by a decrease in the intracellular content of potassium. While the data on the exchangeable potassium are meager, they suggest that the exchangeable potassium content is lowest early in the course of severe or moderately severe rheumatic fever, when the exchangeable sodium content is highest. This change in equilibrium between the intracellular and extracellular compartments does not appear to be reflected by any consistent alterations in the serum concentrations of sodium and potassium.

An increase in capillary permeability usually results in extracellular edema formation; since edema was not evident in the present study, it is concluded that capillary permeability was not significantly altered. Furthermore, no significant changes were noted in the plasma volume or total blood volume. These data suggest that the greatest physiologic abnormality occurred at the level of the cell membrane and that changes in capillary permeability were slight.

Relationship to Immune Mechanism. Recent studies with isotopes have dispelled the previously accepted view that all of the body's store of sodium and chloride is located extracellularly. It is now recognized that a much more complex situation prevails. The concept of cell membranes impermeable to ions has been supplanted by the view that ionic exchange occurs continuously across a membrane that may actively participate in the process by means of its own enzymes and metabolic processes. It is now believed that concentration gradients are maintained by enzymatically controlled intracellular metabolic processes as well as by physicochemical processes. Inorganic ions are known to play a dynamic role as essential components of enzyme systems. The results of the present study suggest that rheumatic fever

produces some alterations in such a dynamic process.

It is apparent that any severe disease process, whether produced by a physical, chemical, or biologic agent, will result in abnormal physiologic changes in the body cells. For instance, an increase in the intracellular content of sodium has been reported in such diverse disease states as infant diarrhea,[10] dietary deficiency of potassium,[11] simian malaria,[12] Rocky Mountain spotted fever,[13] serum sickness,[14] congestive heart failure,[15] and experimental burns and trauma.[16] Thus, an increase in the intracellular content of sodium may be a nonspecific response to injury of any type.

The purpose of the present discussion is not to describe in detail the mechanisms involved in these various types of cell injury, but simply to determine whether the physiologic changes observed in acute rheumatic fever can be satisfactorily explained by the hypothesis that rheumatic fever is a hypersensitivity reaction to streptococcal infection. It was formerly assumed that antigenic substances that were injected parenterally remained in the extracellular fluid compartment. Recent studies with tagged antigens, however, have shown that antigenic substances rapidly cross the cell membrane[17] and localize in the mitochondria.[18] It has been suggested that the mitochondria are the anatomic site of protein synthesis, and that antibody production is a modified form of gamma globulin synthesis. An in vivo intracellular union of antigen and antibody might be expected to produce disturbances in the orderly function of intracellular enzyme systems and alterations in membrane permeability.

In the present study, the evidence of an alteration in cell membrane permeability, without evidence of abnormal capillary permeability, suggests that the changes may be due to the tuberculin or delayed type of hypersensitivity reaction,[19] since an increase in capillary permeability is usually evident in an in vivo anaphylactic type of reaction.

Adrenal cortical hormones, under certain conditions, can suppress antibody formation.[20] Although the exact mechanism of this suppression is not known, it has been stated that these substances tend to restore the integrity of cell membranes.[21] The mechanism of action by which salicylates and aminopyrine suppress the rheumatic symptoms and signs is also unknown, but their effect appears to be more than antipyretic. The increased radiosodium space, for instance, persisted for several weeks after initiation of therapy, whereas the fever usually subsided within 48 hours. It has been suggested that both salicylates[22] and aminopyrine[23] stimulate the adrenal cortical secretion. Whatever the exact mechanism of action may be, the data suggest that the abnormal permeability of cell membranes in acute rheumatic fever can be suppressed by all of the therapeutic agents used.

It is obvious that further and more extensive studies of the type reported here are necessary for a better understanding of the patho-immunophysiology of rheumatic fever.

Summary

Serial measurements of the radiosodium space and the exchangeable sodium and potassium contents were made in 20 patients with acute or chronic active rheumatic fever, during hospitalization and therapy. Ten of 11 patients with severe disease had an initial value for Na^{24} space of more than 330 ml./Kg. of body weight, with no evidence of edema. Most of the subsequent values were lower, at a time when body weight had increased. Such changes were noted infrequently in individuals with mild or moderately severe disease.

The exchangeable sodium content of the body correlated well with the radiosodium space. The exchangeable potassium content of the body tended to be low when the exchangeable sodium content was high. No striking changes were noted in the serum sodium and potassium concentrations.

The results have been interpreted as suggesting that the intracellular content of sodium is increased during acute rheumatic fever, although the possibility of an increase in bone sodium has not been excluded, and that this abnormality may be due to an alteration in the permeability of cell membranes induced by an immune mechanism.

Summario in Interlingua

Mesurationes serial del spatio de natrium radioactive e del contento de excambiabile

natrium e kalium esseva facite in 20 patientes con acute o chronic febre rheumatic. Omnes esseva hospitalisate e sub tractamento. Dece del 11 patientes con grados sever del morbo habeva un valor initial pro le spatio de Na^{24} de plus que 330 ml per kg de peso corporee. Iste patientes habeva nulle signo de edema. Le majoritate de lor valores subsequente esseva plus basse, e isto a un tempore quando le peso corporee habeva accrescite. Tal alterationes esseva notate infrequentemente in individuos con leve o moderatemente sever grados del morbo.

Le contento de excambiabile natrium in le corpore esseva ben correlationate con le spatio de natrium radioactive. Le contento de excambiabile kalium in le corpore monstrava le tendentia de esser basse quando le contento de excambiabile natrium esseva alte. Nulle frappante alterationes esseva notate in le concentrationes seral de natrium e kalium.

Le resultatos pare indicar que le contento intracellular de natrium es augmentate durante acute febre rheumatic, sed le possibilitate non pote esser negligite que il occurre un augmento del contento de natrium in le ossos e que iste anormalitate resulta de un alteration del permeabilitate del membranas cellular como effecto de un mechanismo immunologic.

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PANEL DISCUSSION

GUEST EDITOR: HOWARD B. BURCHELL, M.D.

Selection and Management of Patients for Cardiac Surgery

INDEX

A panel discussion on selection and management of patients for cardiac surgery was conducted in conjunction with the Scientific Session on Clinical Cardiology at Music Hall Auditorium, Cincinnati, Ohio, on Saturday afternoon, October 27, 1956. The panel was comprised of the following members: HOWARD B. BURCHELL, *Rochester, Minn.*, MODERATOR; S. GILBERT BLOUNT, JR., *Denver, Colo.*; MARY ALLEN ENGLE, *New York, N. Y.*; ROBERT E. GROSS, *Boston, Mass.*; WILLIAM LIKOFF, *Philadelphia, Penn.*; C. WALTON LILLEHEI, *Minneapolis. Minn.*

MODERATOR BURCHELL: To begin with, we shall ask Dr. Gross, "At what time of life do you prefer to see the typical patent ductus?"

DR. ROBERT E. GROSS: I think the answer should be related to the experience that the particular surgeon has had. Many years ago we thought the best age was around 4, 5, or 6 years. But now with a larger surgical experience, most surgeons consider that surgery is very satisfactory even down to a year of age. When the diagnosis is quite clear, there seems to be little difficulty in going ahead; certainly there is no good reason for putting things off.

One has to bear in mind, not only the situation of the child, but very often the reaction

of the parents. Sometimes the parents would rather put off surgery if they can, and actually there is little harm in this. In other instances a parent is overly disturbed, and really feels better when the whole thing is done and over with. We find that this type of surgery is being done on younger and younger subjects, with equally good results.

MODERATOR BURCHELL: Dr. Engle, when do you believe that infants should be operated on for coarctation of the aorta?

DR. MARY ALLEN ENGLE: I believe that for the asymptomatic infant with coarctation of the aorta, surgery is not indicated. However, some go into cardiac failure in early infancy. In our experience, most of these babies, who have no other intracardiac lesions, have done well with medical management, directed toward relief of failure and prevention of infection. We believe that if they respond promptly to medical therapy, surgery can be safely postponed until they are larger and the aorta is larger. However, if the baby does not promptly improve, he should be referred for surgery.

MODERATOR BURCHELL: Do you think, Dr. Gross, that the aortic arch syndrome is being recognized throughout the country?

DR. GROSS: I have an idea that many of these anomalies are being overlooked. There are too many subjects, particularly babies, who come to the autopsy table and one finds a double arch or some other important vascular anomaly that could have been treated by surgical measures.

MODERATOR BURCHELL: We have mentioned typical cases of coarctation. May I ask Dr. Blount to tell of some of the complications and say something about pulmonary hypertension with patent ductus?

DR. S. GILBERT BLOUNT, JR.: Relative to coarctation of the aorta, our best observations are from some of the older papers, particularly one published in 1947 by Reifenstein, Levine, and Gross. They concluded that probably 60 to 70 per cent of patients who have a coarctation do not survive beyond the fortieth year of life. About 75 per cent of the deaths were directly related to complications of coarctation of the aorta, while the remaining 25 per cent were from causes unrelated to coarctation.

The deaths directly related to coarctation could roughly be analyzed as follows: about 15 per cent resulted from rupture of the aorta, either the ascending aorta or just distal to the coarcted site; subacute bacterial endocarditis on bicuspid aortic valves or infection at the site of coarctation accounted for many deaths in the past, although since the advent of antimicrobial therapy deaths from this cause have greatly decreased; then cerebral vascular complications claimed a significant number of patients; and finally congestive failure and its complications resulted in the greatest number of deaths in patients with this anomaly.

Regarding patent ductus arteriosus, patients having a small ductus live an uneventful life, although certainly relative to both patent ductus arteriosus and coarctation of the aorta I see many patients with these lesions in the younger age groups, but very, very few patients with either coarctation or patent ductus beyond 45 years of age, and I can only draw one conclusion and that is they are not surviving to the older age groups.

Complications are encountered in patients with a large ductus. Congestive failure may develop very early in life, but this is relatively unusual. The child may be somewhat small and we all talk about systemic starvation. I do not really appreciate the meaning of this term although we assume it reflects inadequacy of the systemic blood flow. Certainly some, after operation, show remarkable increases in growth while others do not. Most of these patients have normal systemic flows at rest. Rupture of the ductus occasionally occurs in infancy, but it certainly is rare. Again, prior to the advent of the antimicrobial agents probably 20 or 25 per cent of these patients died from subacute bacterial endarteritis.

I believe Dr. Gross was one of the first to point out that older individuals with patent ductus never knew what it was to feel good before the closure of their ductus. They had vague complaints, were tired at the end of the day, had nothing really dramatic, but had a very significant improvement in their feeling of well being following surgery.

As far as the development of pulmonary hypertension is concerned, this is a problem that Dr. Edwards discussed at some length this morning. We can say little at this time except that it is my belief that patients who have reversal of flow through their ductus rarely develop this state late in the natural history of the anomaly; that is, it is rare when one observes a patient who has had a continuous murmur of a classical ductus and then over a period of time the condition progresses to reversal of flow with disappearance of the continuous murmur. This can occur on rare occasions, but most of these patients, in my opinion, have significant hypertension from the beginning. I believe this to be related to cross-sectional area of the ductus as compared to that of the aorta below where the ductus enters and, as Dr. Edwards mentioned this morning, a persistence of the fetal pattern of the pulmonary vascular bed occurs that accounts for the pulmonary hypertension that thus develops from earliest infancy.

Moderator Burchell: One of the most exciting developments that we have witnessed in the last few years has been surgery for ventricular septal defects. I'd like to ask Dr. Engle if she has any difficulty in the recognition of ventricular septal defects and if she will tell us of the problems she runs into in the treatment of such defects.

Dr. Engle: It would certainly be untrue to say there is no difficulty in recognizing ventricular septal defects. I think the picture is sufficiently characteristic, though, to allow one to suspect its presence most of the time, particularly if it is a large one. This simple lesion by itself is sufficient to account for a high percentage of deaths in heart failure during infancy. One can suspect this lesion even in a baby in heart failure from the fact that he is not cyanotic, he has a coarse thrill and a harsh systolic murmur maximal in the fourth left interspace, his heart is big and there is more enlargement of the left than the right side of the heart. The left ventricle is the largest chamber radiologically and electrocardiographically. Added to this is a big pulmonary artery and a picture of flooded lungs. Diagnostic possibilities include a ventricular septal defect or a shunt at the aorticopulmonary level. The size of the aorta is then helpful clinically in sorting out the site of the shunt. With a ventricular septal defect, the left-to-right shunt occurs at the ventricular level, so that the aorta receives a smaller blood supply than usual and is smaller than normal. With the shunt at the aorticopulmonary level, whether it is the proximal aorta or is farther along the aortic arch in the region of a patent ductus, the aorta is a big vessel. Thus with left ventricular enlargement and flooded lungs in a pink baby, the size of the aorta can help localize the shunt.

The management of these babies has been most unsatisfactory from a medical point of view. When I see such patients with heart failure at 3 or 4 months of age, there is no way to predict which will survive. Most will not. This is the time when there is the greatest need for surgical technics such as Dr. Lillehei has developed and will talk about.

Before surgery is considered in such a baby or in older patients, I think cardiac catheterization should be performed. The purpose is not only to document the lesion and its effects right now but to have the studies as a base line for future evaluation so we can learn more about the condition: what the optimal situation for surgery is, what can be helped and what cannot be helped.

Moderator Burchell: That immediately brings us to Dr. Lillehei. He probably has 3 things he could start discussing: (1) the need for catheterization before his surgical procedure, (2) the time he would choose for elective operation, and (3) what constitutes an emergency or semi-emergency situation.

Dr. C. Walton Lillehei: Intracardiac surgery is a relatively new field of surgical endeavor and at this stage of our experience and knowledge I have considered it of value to establish the diagnosis as precisely as possible in all cases beforehand by cardiac catheterization. There are several reasons for this. First, operating time for use of the pump-oxygenator remains at a premium due to the large backlog of patients awaiting treatment, and precise preoperative diagnosis avoids confusing isolated ventricular defects with other

conditions for which the perfusion system is not needed, such as a patent ductus arteriosus with severe pulmonary hypertension and pulmonary insufficiency.

Secondly, cardiac catheterization by objective measurement of intracardiac pressures and flows is providing valuable and interesting information on the genesis of the physiologic abnormalities resulting from these defects as well as the rate and degree of their regression after corrective surgery.

Finally, these physiologic evaluations have some value in predicting operative risk. However, without going into detail I should hasten to add that we have found early in our experience that the severity of the physiologic changes for a given patient has not correlated nearly as closely with operative risk as has the status of the patient's pulmonary vascular system as determined by microscopic study of the arterioles in a lung biopsy.

The next 2 questions, namely, the time for elective surgery and emergency or urgent indications for reparative surgery, can probably be best answered together. Dr. Engle has already emphasized the fact that ventricular septal defects are a serious threat to life in the substantial majority of patients born with them. Perhaps 50 per cent of these patients die of their defect in the first 12 months of life, and since it is such a common defect one sees in practice a good many rather desperately ill infants with such findings as failure to gain weight, persistent decompensation, resistance to medical treatment, and repeated pneumonias. Virtually all these infants already have severe pulmonary hypertension due to varying combinations of the 2 factors of increased pulmonary flow and increased pulmonary vascular resistance. These patients we consider as urgent candidates for corrective surgery, since nearly all are marked for death unless successful reparative surgery can be carried out. In fact, in one such extreme instance, we closed a ventricular septal defect in an 8-week-old infant utilizing the pump-oxygenator as an emergency procedure in the middle of the night because of our cardiologists' opinion that the child was terminal and would not likely survive until morning. In this case the diagnosis, which was correct, was entirely clinical, since the infant was deemed too ill to undergo catheterization when first seen.

On the other hand, if we see an infant with a ventricular septal defect who is gaining weight normally or at least nearly normally and who appears to be responding well to medical management, we would prefer to delay corrective surgery, if possible, until at least 18 months of age.

The closure of ventricular defects even in the tiniest infants is technically quite easy. The defects are nearly always small and usually easily closed by stitches only (these defects grow in size as the patient grows). However, the principle problem in these patients has been the management of the postoperative respiratory complications occurring or existing in their damaged lungs. Even normal infants have, at best, a very limited respiratory reserve. In these frail infants with severe defects the problem of management of the inevitable secretions accumulating in their tiny bronchi assumes major proportions. An infant's lack of chest muscular development and its inability to tolerate any dyspnea for long also need to be reckoned with in this regard. However, as these problems have been recognized and attention devoted to them, substantial progress has been made as indicated by a steadily declining risk in this age group.

In the older children the presence of severe pulmonary hypertension (the pulmonary artery pressure exceeding 70 per cent of the aortic) is an ominous sign and certainly such patients are considered as urgent candidates for reparative surgery. In patients with severe pulmonary hypertension we find with the passage of time steadily increasing percentages with severe intimal proliferation in their pulmonary arterioles.

Moreover, even the relatively uncommon patients with ventricular shunts and without appreciable hypertension need very close observation if corrective surgery is not carried out, since in some the pulmonary pressure may double itself each year for several years until it has reached systemic levels.

We do see a few patients, nearly always children, who have a ventricular septal defect

with a substantial left-to-right shunt, but without appreciable pulmonary hypertension. The risk of corrective surgery utilizing the pump-oxygenator in them is very low because of their undamaged lungs and good cardiac reserve and we recommend closure at an elective date usually during their summer school vacations in the same way and for the same reasons that one would advise in a patient with a patent ductus arteriosus with similar findings.

In conclusion, I should like to emphasize that patients with ventricular defects have, in reality, 2 diseases. The most dramatic and the one that has attracted our attention for so long in the past was the intracardiac defect and methods for reaching it in order to close it. Paradoxically, we now find that our greatest problem is not the correction of their anatomic defects within the heart, which is nearly always straightforward, but rather the management of their secondary disease, which so many have, namely, pulmonary hypertension and arteriosclerosis.

MODERATOR BURCHELL: Is there a member of the panel who would like to ask Dr. Lillehei a question at this time, or volunteer any comment?

DR. GROSS: I would like to ask a question, because as Dr. Lillehei has indicated, small babies are difficult to operate on for many reasons. Is it possible one could perform a palliative procedure early in the game, such as partially constricting the pulmonary artery by a band, to gain time, and then proceed with a curative attack later on?

DR. LILLEHEI: Yes, this procedure makes some sense at least theoretically and I believe that some should explore the results with it. However, I personally have no interest in such a palliative approach when we now have a curative operation available. There are several practical reasons for this attitude. First, reoperations upon the heart utilizing the pump-oxygenator are frightfully difficult due to the necessity of tearing down old adhesions in a heparinized patient as well as the obfuscation of valuable landmarks by these same adhesions.

Moreover, in the dog we have had a considerable experience in producing pulmonary stenosis. It has never been possible to produce, in 1 stage, a significant degree of stenosis. If we did, the animal succumbed. In these animals in which an appreciable degree of pulmonary stenosis has been produced successfully, it has been necessary to do a series of operations allowing the animal time to adapt to each added increment of stenosis.

In addition, we have had the opportunity of operating upon for cure several patients with ventricular defects who had had banding of their main pulmonary artery previously. It was remarkable that in not one of these patients was there the slightest stenosis of the pulmonary artery remaining, although the extensive adhesions present testified to the previous surgical procedures.

Finally, as I implied earlier, solid progress has been made in the management of the pulmonary complications of these cardiac lesions as we have learned to appreciate their significance. Actually most of these pulmonary problems are not new ones but rather old problems in a new disguise. We have met them by constant vigilance in the early postoperative period. A special nurse is not enough; rather the continuous presence of a physician experienced in the detection of both impending medical or surgical complications has been invaluable. In selected instances appropriate use of tracheotomy or mechanical respirators has been lifesaving.

DR. WILLIAM LIKOFF: I would like to ask Dr. Lillehei if the attrition in the first year of life with ventricular septal defect is better or worse than the mortality and morbidity associated with its correction. Furthermore, can he provide us with a guidepost as to the indications for its correction.

DR. LILLEHEI: Yes, based upon experience with a considerable number of infants, approaching 40 to 45, I believe that an infant who is doing poorly has a much better chance of being cured with early reparative surgery. Moreover and more important, I believe our cardiologists are convinced of this, based upon their independent observations of the results of early reparative surgery. As a result, one of our present problems is concerned with getting these infants scheduled for surgery promptly.

It seems that they are still being born at a faster rate than we have been able to take care of them by operation.

MODERATOR BURCHELL: Now we shall pass on to atrial septal defects. Dr. Likoff, would you tell us what you do with the patient who comes with a typical atrial septal defect and with the patient whose defect isn't so typical?

DR. LIKOFF: It is proper to record a changing attitude concerning the surgical correction of this defect.

At the outset surgery was reserved for those at the end of their clinical deterioration. Pulmonary hypertension actually was considered a major indication for surgery.

Currently, the indications are based on anatomic and physiologic considerations.

The operation is performed when the defect is of the secundum type and singular. It is best corrected when there is an absence of pulmonary hypertension and when the left-to-right shunt is predominant or is in excess of the right-to-left shunt by at least 1.5 liters. Finally the indications for surgery must be related to the dexterity and skill of the surgeon so that the contemplated mortality and morbidity are far less than the ordinary devolutionary pattern associated with this defect.

MODERATOR BURCHELL: Dr. Gross, have you a comment?

DR. GROSS: I thoroughly agree with Dr. Likoff; as things get better in surgical statistics, one becomes more justified in accepting cases where there has been less and less trouble in the clinical picture.

In the past we have preferred to operate on only those patients who had these very high left-to-right flows through an atrial septal defect, with the right ventricle performing several times the work of the left ventricle. But as things have gone on, we have lowered our sights a great deal. And I have no doubt as we go along we will be accepting smaller and smaller shunts for surgery because the picture has been so good as far as correction is concerned.

This is not considered a major problem in childhood, but I would like you to comment on that.

DR. ENGLE: That is true. If it is not a part of a common atrioventricular canal, almost categorically one can say that infants and children with atrial septal defects do well. If one could predict an age of optimal operability right now, I would say it is somewhere between 10 and 15 years of age, because the period of infancy and childhood in general is so benign and the pulmonary vascular changes that make these patients poor risks later on in adult life rarely take place by that age. As there is wider surgical experience in this condition, I think that just as for a patent ductus, diagnosis of the condition will become the indication for surgery. I don't believe that stage has yet arrived, except perhaps in a few clinics where the mortality rate is quite low. For these reasons I would not select children as the first patients early in a series where surgery on atrial septal defects is just beginning.

MODERATOR BURCHELL: Dr. Blount, I have left an important job to you, and that is for you to tell us how you recognize an acquired lesion of the mitral valve in association with atrial septal defect.

DR. BLOUNT: The differential diagnosis between the ostium secundum defect and so-called ostium primum defect may be a difficult one, although we believe that in general the presence of the primum defect may be detected in most instances. Possibly we had better state at this point that certain observers including Drs. Burchell and Edwards believe that this is not a true distinction and that we should speak of these as variants of the atrioventricularis communis defect. I certainly would have no argument with this; and those have been divided roughly into 3 types. One group is that in which the defect in the atrial septum is low with no remnant of the atrial septum above the valves but no involvement of the atrioventricular valves. Some believe this to be extremely rare and question the entity.

The second group is where there is the low atrial septal defect with no remnant of atrial septum above the atrioventricular valves and with deformities of these valves. The presence of a cleft in the anterior leaflet of the mitral valve is the most common defect but the tricuspid valve may also be deformed.

The third group is that in which we have a

defect in the membranous portion of the ventricular septum plus a defect in the lower portion of the atrial septum.

At the present time, most of the patients that we have studied have not had defects in the ventricular septum; so for the purpose of this discussion we will only consider the group that have an intact ventricular septum, because these are the patients presenting the problem and who must be differentiated from the patient with the secundum defect of the atrial septum. This is of importance because of the greater technical difficulties entailed in closing the primum defect as compared to the relatively simple problem of closure of the secundum defect.

The history is rarely of help. By and large the patient who has involvement of the atrioventricular valves may do somewhat more poorly during early years of life. Whenever a high-pitched blowing systolic murmur is heard along the lower sternal border or mitral area one should immediately be suspicious of the presence of the A-V communis lesion, that is, the so-called ostium primum lesion.

It is important to decide whether this murmur is due to mitral insufficiency or tricuspid insufficiency. I have observed patients rejected for surgery because of a systolic murmur over the mitral area, and considered to reflect mitral insufficiency and therefore a primum type defect, when actually this murmur reflected functional insufficiency of the tricuspid valve due to great dilatation of the right ventricle. With rotation of the heart the murmur is transmitted to the apical area or what we consider the mitral area. When the murmur is due to mitral insufficiency an ostium primum defect would be considered but if due to tricuspid insufficiency a simple secundum defect might well be present.

Fluoroscopy is of very little help. Certainly we all realize that with a large globular heart it is most difficult if not impossible to differentiate the degree of left ventricular enlargement that might be present from the extent of the right ventricular enlargement.

Electrocardiogram offers important evidence and I think if we suspect the presence of the primum type defect from the auscultatory findings then the evaluation of the electrocardiogram may give additional evidence suggesting that one is not confronted with a straightforward secundum type defect. The findings of left axis deviation in the standard limb lead and a horizontal electric position in the unipolar limb lead should immediately arouse serious doubt as to the presence of a secundum type defect and suggest the presence of a primum type defect. The precordial leads may in addition reveal findings suggestive of hypertrophy of the left ventricle. Thus the auscultatory findings when considered with the electrocardiogram frequently give rise to sufficient evidence to indicate the presence of a form of an atrioventricularis communis lesion.

As far as catheterization is concerned, there are several findings that may be somewhat helpful, but certainly are not diagnostic in individual cases. The fact that the catheter passes across into the left side of the heart at a lower level than usual is only suggestive. Also, if you pass the catheter out into a pulmonary vein and then attempt to advance it a little it may buckle and the loop may sag to a lower position within the heart shadow than one usually observes. The catheter may enter the left ventricle more readily and more frequently in the primum defect but in the individual case this is not helpful.

MODERATOR BURCHELL: Dr. Lillehei, have you any comment on the problem?

DR. LILLEHEI: Dr. Blount has reviewed the valuable criteria usually of value in distinguishing between an atrial defect of the secundum type and the various forms of the ostium primum syndrome. At a time when we were repairing atrial secundum defects under direct vision, utilizing hypothermia, this differentiation was of life or death significance to the patient as is the situation also if one is utilizing one of the closed or blind technics that have been advocated for secundum type atrial defects.

Suffice it to say, accurate differentiation is not possible in every case, regardless of the skill and experience of the diagnostician.

This fact means that in a certain number of patients when he uses hypothermia or one of the above-mentioned blind technics for closure

of atrial septal defects, the surgeon will find himself in the operating room with the chest open and at the mercy of the more complicated pathology found to be present.

This is true because it is possible to deal curatively with the atrioventricularis communis defects (ostium primum syndrome) only if one has available a pump-oxygenator and total cardiopulmonary bypass. With hypothermia or a closed method the patient, in this situation, is doomed to death or at best, if he survives, to a thoracotomy that not only served no purpose but actually impaired his chances for successful curative surgery at a later time with the pump-oxygenator.

This consideration is so vital to the patient's well-being that some months ago we changed to the use of total cardiopulmonary bypass with the pump-oxygenator for repair of all atrial septal defects. The dividends of this policy have been numerous and gratifying. First, in a substantial series of atrial secundum defects there have been no deaths. The ability to close even these simple defects in an unhurried and precise manner with interrupted stitches indicates that the percentage of anatomic cures may be expected to approach 100 per cent. And finally, we have encountered unexpectedly complicated secundum defects that could be repaired completely with ease. In 1 such patient, with drainage of the right pulmonary veins into the superior vena cava and a foramen ovale defect, the repair although straightforward required a cardiac bypass interval of 55 minutes. Moreover, we have encountered ostium primum lesions in several patients where there was absolutely no reason to suspect preoperatively more than a secundum lesion.

It is quite predictable that other cardiologists and surgeons will, as they acquire confidence in their pump-oxygenator, abandon completely the less satisfactory methods that have been advocated in the past for closure of atrial septal defects.

DR. LIKOFF: In echoing Dr. Lillehei's experiences I would like to state that the criteria outlined by Dr. Blount were not satisfactory in identifying over half of our patients who had septum primum.

There just had to be a period in this panel when we would part company, and I suppose this is as good a place as any.

MODERATOR BURCHELL: That is what we want. I think we should go on, however, to the problem of pulmonary stenosis of the isolated type. I'd like Dr. Gross to sum up the present attitude of surgeons and his own attitude concerning this problem.

DR. GROSS: I am sure that not all individuals with pulmonary stenosis need be operated on. There are certainly all grades of these obstructions. When the block is mild, the patient generally has a rather good prognosis, and surgery is not justified. How often do these mild forms occur? I would say about half the patients that I have seen have not been operated upon because we thought the obstruction was so mild. Doubtless there are also many others with a mild sort of anomaly who never even got to a surgeon for review.

The question comes, "Where does one draw the line between those you want to operate upon, and those you don't?" Certainly, if there are symptoms, there is no hesitation about advising surgery, but there is a great group of patients in whom there are no symptoms as yet, and yet they have been shown (by catheterization) to have a high degree of block. We have considered that if the right ventricular pressures hover around 90 or 100, surgery is desirable: certainly if the pressures are about 140 or 150, surgery should be strongly advised.

DR. ENGLE: This is related, just as Dr. Gross implied, to the severity of the stenosis. I'd like to add a point to what Dr. Gross mentioned. He commented that many of the patients he sees are asymptomatic and have only a mild degree of block, so that the surgeon does not operate on them. I'd like to add that this is a progressive condition. The patient should not be lost sight of, but should be re-evaluated periodically for evidence of increasing severity of stenosis.

Those who have severe degrees of stenosis may present even in the first few days of life with great right ventricular enlargement, right atrial enlargement, and heart failure. Early in life, the foramen ovale is usually

patent; a right-to-left shunt occurs through it if the stenosis is severe. These are "blue babies," who should be operated upon if recognized at that time.

It is unusual for the condition to be so severe this early in life. The more typical picture is that of a child who is not cyanotic and does relatively well until he is in school. Then as he grows larger and more active, he finds he cannot keep up with his playmates because he gets short of breath and has to rest. Examination reveals a pulmonary systolic murmur and diminished second sound, and an electrocardiographic pattern of right ventricular hypertrophy even though the over-all heart size may not be enlarged.

What one does then depends not only on the severity but also on the site of stenosis. The electrocardiogram is one of the best indices of severity. If the V leads show right ventricular "strain" in addition to hypertrophy, this indicates severe stenosis even though the patient has few symptoms and not much cardiac enlargement. The right ventricular pressure then is in excess of 125 mm.

Fortunately the obstruction in isolated pulmonary stenosis is almost always at the pulmonary valve, rather than within the right ventricle at various subvalvular levels. The far greater frequency of valvular stenosis is fortunate, since it can be operated on with greater success than infundibular stenosis. This latter situation is changing with newer technics of surgery that Dr. Lillehei and Dr. Gross will speak about.

The differentiation of valvular from subvalvular stenosis depends both on clinical findings and catheterization. The 2 most helpful clinical features are the location of the murmur and the presence or absence of dilatation of the main pulmonary artery. The murmur of valvular stenosis is maximal high in the first and second left interspaces, in contrast to infundibular obstruction where the thrill and murmur are lower down over the heart along the third and fourth left interspaces. Poststenotic dilatation of the main pulmonary artery is present with valvular pulmonary stenosis but absent with infundibular obstruction. Cardiac catheterization has been more helpful in my experience than angiocardiography in deciding the issue.

MODERATOR BURCHELL: Dr. Blount, can you make this differentiation?

DR. BLOUNT: Could I say one more word on the ostium primum defect? I'd like to help Dr. Likoff.

I think that we ought to make one thing clear, and that is that it is not the location of the atrial septal defect that is responsible for the deviations from the classical findings of the secundum defect. It is the involvement of the atrioventricular valves with the resulting insufficiency of these valves that gives rise to the variations from the secundum picture and thereby makes possible the differential diagnosis.

The differential diagnosis between valvular and infundibular stenosis can be established by careful clinical evaluation in the majority of cases. However, when occasionally they occur together, and this is difficult to establish, you begin to think you have this problem solved, you then encounter a patient who reveals that this differential diagnosis may not always be possible. It might be well to state that I believe that infundibular stenosis with an intact septum is extremely rare and I would never be certain that the patient had this until the heart was carefully examined and in hand. A defect in the ventricular septum is almost always present although at times it may be so small that it will be missed even after cardiac catheterization and angiocardiographic evaluation.

The presence of a poststenotic dilatation of the main pulmonary artery is in general a valuable finding and of course strongly suggests valvular stenosis. However, I have observed a fair number of valvular stenoses that did not reveal this due to positional changes or other reasons and there is some reservation in the minds of some observers that this is not just due to the turbulence of flow, but that it may be due to other causes such as secondary or primary disease alterations in the pulmonary artery that predispose to this state. Certainly the degree of the poststenotic dilatation, at least in our experience, does not correlate with the severity of the stenosis.

Careful auscultation offers much in this differential diagnosis and I learned much from Dr. Aubrey Leatham concerning some of the finer points in valvular pulmonary stenosis.* Frequently in valvular stenosis one can detect an early systolic ejection sound. Also, with valvular pulmonary stenosis, frequently the second sound is split and it may be quite widely duplicated. There appears to be a definite relationship, as Dr. Leatham has shown, between the wideness of the split and the right ventricular pressure. The higher the right ventricular pressure the wider the duplication, and the less prominent the second component, and this is something we do not usually hear or find on phonocardiography in infundibular stenosis.

Dr. Gross: I'd like to make 2 comments. First, there is the question of dilatation of the pulmonary artery beyond a stenosed valve. In older subjects, where the x-ray man can pick it up very nicely, pulmonary artery dilatation is a valuable finding; but we have been fooled many times on subjects who are only a year or 2 of age. In these small subjects the roentgenologist might not see any dilatation of the pulmonary artery, but yet at the operating table we frequently find that there is actually a valvular stenosis and that the pulmonary artery is beginning to dilate. Hence we think that in the very young subject the failure of a roentgenologist to find pulmonary artery dilatation does not necessarily rule out valvular stenosis.

The second point I think important to bring out is the question of when to refer people for surgery. We have had the experience several times of having youngsters, in mid childhood, with absolutely no symptoms, but we know by catheter studies that they have enormous pressures in the right ventricle; operation has been advised, but the family has refused this. We have had the sad experience of finding some months (or a year or 2) later that such a youngster comes back in failure.

There is a great difference in operating upon those 2 types of cases. We all know that for the average case (without any failure in the picture) the surgeon offers a great deal and with a risk that is almost zero. But to operate upon those who are in failure brings very high surgical fatality rates. These points emphasize the belief that we should operate upon patients *before* they get into failure.

Moderator Burchell: Dr. Lillehei, you haven't had a chance to express yourself on this.

Dr. Lillehei: Pulmonary stenosis, whether it be valvular or infundibular, is theoretically a completely curable lesion. Thus, complete cure is the only acceptable and logical goal for surgeons and cardiologists. Yet, in every series of patients that I am aware of treated by closed or blind methods, including our own series, from 30 to 60 per cent of the patients have remained uncured. Without going into great detail the reasons for this unsatisfactory state of affairs are twofold: First, incomplete or inaccurate division of the pulmonary valve, and secondly, failure to recognize or to correct associated defects such as infundibular stenosis, atrial, or ventricular septal defects.

Hypothermia allows the pulmonary valve to be divided accurately under direct vision, but the method falls down badly when one attempts to correct the associated defects frequently encountered in these patients.

About a year ago it became obvious to me that one can approach more closely this goal of complete cure for patients with pulmonary stenosis by use of the cardiac bypass method with the pump-oxygenator. The procedure has been adopted by us for all patients undergoing surgical management for pulmonic stenosis at the Heart Hospital.

The benefits to the patient, by this approach, have been convincing.

Moderator Burchell: Dr. Gross, could you tell us something of your experience with congenital aortic stenosis?

Dr. Gross: I hate to do it because it hasn't been very good. Maybe somebody else could sound a little better note.

A ventricle that is blocked can come to failure, and once failure has appeared it is

* The harsh systolic murmur is frequently loudest in the first intercostal space at the left sternal border and always louder in the first than in the third left intercostal space.

difficult to reverse it. Closed surgical technics for treating congenital aortic stenosis are very poor and are now old-fashioned. I hope that the newer technics with open approaches will improve matters.

MODERATOR BURCHELL: Dr. Likoff, would you like to say something about the diagnosis of this?

DR. LIKOFF: Some of the diagnostic signs that differentiate infundibular from valvular pulmonary stenosis are applicable in differentiating subaortic from valvular stenosis.

Valvular aortic stenosis is more common and is associated with dilatation of the aorta. The latter is not present in subaortic stenosis. The second sound is diminished in valvular and is normal in subaortic stenosis.

Unfortunately the operative interference, particularly in congenital aortic valve stenosis, is associated with the very real risk of producing dynamic aortic insufficiency, particularly if blind technics are used.

DR. ENGLE: I have nothing to add but would like to echo the thought that aortic valvular stenosis, like pulmonary, is much more common than the subvalvular type. I would vote for operation under direct vision.

DR. BLOUNT: I certainly would agree with the previous speakers that in our experience also valvular stenosis is encountered more often than subvalvular stenosis. I think the approach from above through the open aorta under conditions of circulatory occlusion and a dry, clean operative field offers one a much greater opportunity to correct this defect. At the present time we have operated upon 7 patients with a diagnosis of congenital aortic valvular stenosis. Two turned out at surgery to have the obstruction at the subaortic level. Technically in the patients with valvular stenosis there has been no difficulty and auscultatory evidence of aortic insufficiency has been noted in but 1 patient.

As to differential diagnosis, I am certain we all believe it to be very difficult. One finding that may be of importance but certainly is going to take a much greater number of patients for evaluation is the site of the poststenotic dilatation. In both patients having subaortic stenosis the dilatation appeared to be maximum in the area of the sinuses of Valsalva, whereas when the stenosis was valvular the dilatation appeared to be distal to the sinuses.

DR. LILLEHEI: Patients with aortic stenosis, either congenital or acquired, deemed in need of surgical management are best treated by an open method utilizing total cardiopulmonary bypass and the pump-oxygenator. The exposure of the aortic valve is via the aorta.

It is probably essential that the congenital aortic lesions be operated upon by a visual method because the results have been uniformly poor in those treated by closed methods due to the likelihood of production of aortic insufficiency in the valvular lesions and the inability to relieve adequately the infundibular obstructions in the subvalvular type. In our own experience, the subvalvular obstructions have occurred often enough, actually in 2 out of 5 cases, to indicate that they are not rare.

One other word that I would like to say about aortic stenosis is to emphasize its treacherous nature. I am chagrined to say that within the past 2 months 2 infants died suddenly on our hospital wards and at autopsy were found to have severe valvular aortic stenosis. In neither was the diagnosis made during life although in 1 it was suspected along with several other possibilities. In both of these babies the murmur was very soft and there was no thrill, doubtless because so little blood was entering the aorta. The fact that the classical clinical signs of aortic stenosis may be lacking or insignificant when the stenosis is very tight is worthy of emphasis.

MODERATOR BURCHELL: Dr. Lillehei, I'd like you to say something about the general position of surgeons at the present time, and also in the future, concerning severe intracardiac defects such as transposition of the great vessels.

DR. LILLFHEI: The present advance in cardiac surgery has been the development of the open operation in which the surgeon sees precisely what needs to be done and then proceeds to do it under direct vision. This accomplishment has resulted in the possibility of a fuller life to many who were previously disabled. Open heart surgery is a relatively

new field of surgical endeavor yet one that obviously is destined to continue to grow at a rapidly progressive rate because of the impressive benefits accruing to the patients with remediable heart disease.

Yet there are plenty of horizons left in this field and perhaps one of the most pressing is the development of a curative procedure for complete transposition of the great vessels. It is altogether too common a lesion to allow for any peacefulness of mind. It heads most all lists as the most common cause of neonatal death and death in the first year of life.

Several years ago a survey of our own experience indicated that 80 per cent of patients dying with complete transposition of the great vessels were dead by their first birthday.

However, there are several aspects of the problem that have favorable portent for the future. First, it is a relatively easy lesion to recognize and even physicians who have only a passing acquaintance with the problem often can make the diagnosis. Another fortunate aspect of the lesion is that the infants are usually born in good condition and they rarely die in the first 2 or 3 weeks of life, so that there is ample time to recognize these patients and to carry out treatment as soon as we have a satisfactory procedure to recommend. Finally, those babies with complete transposition who are the most seriously ill and die the soonest are paradoxically the best surgical risks for a completely corrective procedure because they have the fewest associated defects.

In the past, we have given the palliative procedures for complete transposition a fair trial and quite frankly I do not believe they are worth doing. The most promising of these was transplanting the pulmonary veins to the right atrium and transplanting 1 or more vena cava to the left atrium in stages. Whereas 32 such patients had 1 or more of these procedures carried out, when we assessed them 2 years later, only 7 were still alive. This terminated our interest in the palliative approaches and since that time we have devoted ourselves to devising an operative procedure that will be physiologically curative, if possible, and technically feasible. Such an approach involves utilizing the pump-oxygenator. Five patients have been operated upon to date by this method and while I am sorry to say we have not had any complete cures as yet, I remain very optimistic, on the basis of what we have learned to date, about the future of this approach.

MODERATOR BURCHELL: Dr. Engle, would you like to indicate the salient points in the recognition of this in infancy?

DR. ENGLE: They consist of a cyanotic child with increased pulmonary blood flow, an enlarged heart, and characteristic changes at the base of the heart that indicate the great vessels do not have a normal origin. One sees a cavity in the region where the main pulmonary artery should arise and in the frontal view of the heart, a very narrow basal shadow that on rotation of the patient into the oblique positions becomes quite broad. This is in contrast to the normal situation where the 2 vessels are side by side and produce a base that is equally broad in all projections, and it is in contrast to 1 condition that may simulate it: a common truncus arteriosus, where there is 1 big vessel at the base of the heart in all views. The electrocardiogram shows right ventricular hypertrophy. Murmurs may be absent.

MODERATOR BURCHELL: We have 7 minutes left and we had hoped to get along to some acquired cardiac conditions. I am going to ask Dr. Likoff to comment on the recognition of the predominant lesion when mitral insufficiency and mitral stenosis coexist.

We have had some advance talks on this already today, but I should like to have him discuss this a little. Then perhaps the other members of the panel may ask questions of him, or give their own experiences.

DR. LIKOFF: In examining this differential diagnosis it is wise to reflect on the areas of difficulty and why they arise.

From an auscultatory viewpoint mitral stenosis may exist without the characteristic findings classically expected. However, this is a minor point upon which to base a differential diagnosis where the valve is immobile and the first mitral sound may be normal and midlate diastolic murmur most difficult to recognize. Furthermore, in the presence of tricuspid in-

sufficiency a systolic murmur may be present in the mitral area that may be mistaken for mitral insufficiency. Hence, it is not unusual for a tight mitral stenosis to masquerade as mitral insufficiency.

Secondly, the x-ray contour of the heart in both lesions surprisingly enough may be quite similar.

Thirdly, mitral insufficiency may actually produce the electrocardiographic and x-ray evidence of right ventricular hypertrophy even when it exists as a solitary lesion.

The areas of overlapping in objective methods of study are duplicated in the symptomatology. It is admissible that patients with mitral insufficiency are less likely to have pulmonary or peripheral embolization.

In an attempt to establish a satisfactory difference between mitral stenosis and mitral insufficiency or to determine which of both lesions is predominant, we are now relying upon 2 basic methods of study. The first is left heart catheterization. If an adequate gradient is indicated across the valve, it is logical to presume that significant obstruction is present. At the same time the presence of the contour wave of mitral insufficiency will indicate its anatomic presence, but not its quantitative degree.

The second objective study is the ventriculogram, which requires the insertion of dye directly into the left ventricle. The regurgitation of dye into the left atrium can be quantitated crudely. This study is suprisingly easy and safe.

In conclusion one is required to rely upon many methods of investigation for the difference and although the difficulties are great, an accurate appraisal is possible.

Postscript by Dr. Burchell

The discussion of the panel was recorded by Stenotype at the time of the scientific sessions and a copy was submitted to each panel member for correction. The main goal of the panel was to advise the practitioner concerning selection of patients for cardiac surgery rather than details of management. The questions posed were arranged in the hope that each panel member might clarify the problems of recognition and disposition of cardiac defects amenable to surgical treatment. Many problems in diagnosis and treatment, because of limitation of time and varied special interests of the audience, were never touched upon; for these serious omissions, the interested reader should consult the writings of the various panel members. With the rapidly expanding field of surgical therapy for a multitude of cardiac defects, it would be readily apparent that considerable controversy would exist regarding the best advice to be given to a patient. It is particularly when reconstructive intracardiac operations are done with the aid of a heart-lung bypass that the best advice today may be outmoded within a year. If time had allowed, more controversial current issues might have been introduced into the discussion in which the moderator would have enjoyed participating actively.

CLINICAL PROGRESS

Cardiac Pain

Anatomic Pathways and Physiologic Mechanisms

By JAMES C. WHITE, M.D.

WILLIAM HARVEY demonstrated to Charles I that the heart was insensitive to pain.[1] The subject of this observation was the son of Count Montgomery, a young man who had miraculously survived an injury to his ribs and costal cartilages that left the beating heart exposed in an open cavity. Harvey observed that neither pricking nor pinching the epicardium evoked any sensation of discomfort. Two and a half centuries later, after the advent of local anesthesia, Lennander[2] concluded that the intestines were likewise insensitive, because his patients at operation did not complain of any discomfort on pricking, cutting, or burning of these structures. These misconceptions arose because of the paucity of sensory endings in the heart and other internal organs. Spatial summation is necessary to activate a sufficient number of nerve fibers in order to breach the sensory threshold. Therefore a massive stimulus to a large area of intestinal wall or myocardium is required. When pain is evoked, it is likely to be peculiarly disagreeable, but difficult to describe and to localize. The normal physiologic stimulus for intestinal pain is distention[3] and for the heart ischemia of the myocardium.[4]

François-Franck,[5] professor of physiology in Paris, suggested in 1899 that sympathectomy be done for the relief of angina pectoris. For this purpose cervical sympathectomy was first carried out by Jonnesco in Bucharest in 1916.[6] A decade later Fontaine[7] and Cutler,[8] after reviewing a large number of case reports, found that this operation had given satisfactory relief of anginal attacks in only 60 per cent of the published cases. After further study of the sympathetic innervation and the discovery of the thoracic cardiac nerves, it was established that the characteristic pain in the precordium and arms can be effectively relieved. Cardiac pain is not transmitted by the vagus. Direct stimulation of its trunk in the human patient suffering from angina pectoris (René Leriche, personal communication) has failed to evoke an attack, and bilateral vagotomy in the dog did not prevent pain induced by experimental coronary occlusion.[9] In our consideration of cardiac pain it is therefore most important to describe the sensory fibers that accompany the sympathetic cardiac rami and that must all enter the upper thoracic segments of the spinal cord over its posterior roots.

A final point of interest that deserves mention here is the method of tracking pain fibers. This purpose unfortunately cannot be accomplished by the ordinary method of severing a spinal nerve distal to its posterior root ganglion and tracing the course of its degenerating axons by the Marchi method. The majority of axons that transmit painful impulses to viscera belong to the C fiber group of Gasser and Erlanger.[10] These are not myelinated and therefore do not take the osmic acid stain for degenerating myelin. The cardiac nerves have been studied in great detail by modern anatomists[11] and their content of sensory fibers has been verified unequivocally by physiologic testing in the dog[9] and by many observations after various types of cardiac denervation in man.

ANATOMY OF CARDIAC PAIN PATHWAYS

Sensory Nerve Endings and Terminal Fibers in the Heart

Mitchell[11] has illustrated numerous undifferentiated and fine beaded nerve fibers in the walls of the heart. As he stated, "they are best

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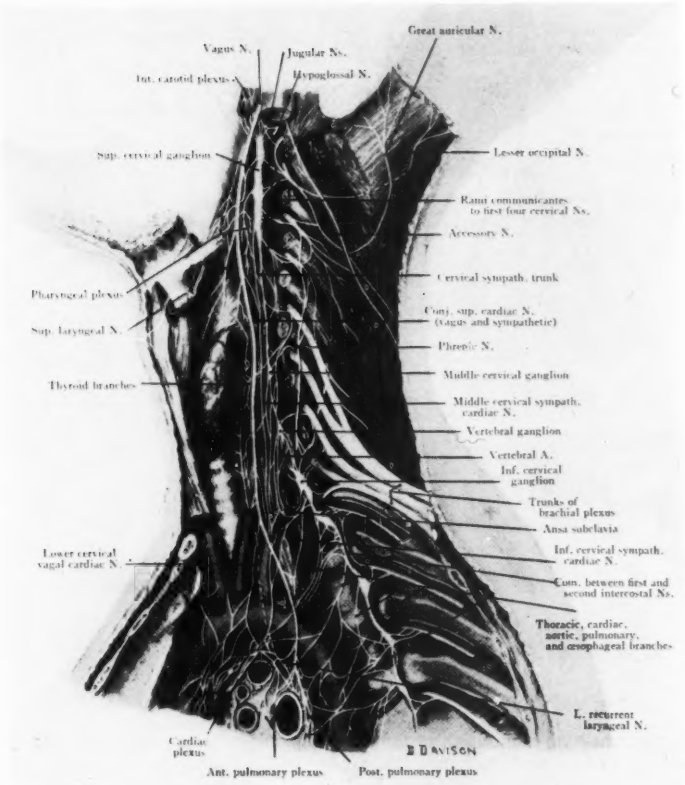

FIG. 1. The cardiac plexus. Reproduced from Mitchell's *Cardiovascular Innervation*[11] with the kind permission of the author and publishers, E. & S. Livingstone, Edinburgh.

seen in adventitia, but finer plexuses appear in the media and intima, or perhaps just deep to the intima or endocardium. Of course these networks, especially those in the adventitia, are composed of afferent and efferent fibres, but in the special receptor areas the proportion of thicker and presumed afferent fibres is unusually high." No encapsulated endings have ever been detected in primate hearts, but the fine beaded terminals are similar to those that are concerned with reception of painful stimuli in the skin and cornea. Many of the fine strands may be sympathetic efferent fibers concerned with cardiac acceleration and others belong to the vagus, but some are certainly terminal sensory axons and are capable of transmitting pain. Some of the afferent fibers in their proximal course along the coronary plexuses develop a certain degree of myelinization. Nettleship[12] was able to demonstrate degeneration of these fibers after resecting the dorsal root ganglia of the upper thoracic spinal nerves. On the contrary, few degenerated after vagal section. It is unfortunate that the majority of pain fibers are unmyelinated and therefore cannot be traced by the Marchi method.

Cardiac Plexuses

The cardiac plexus is situated above the base of the heart between the aortic arch and the bifurcation of the trachea (fig. 1). The superficial portion lies in the concavity of the arch and the deeper part of the plexus behind it. According to Mitchell[11] the superior cardiac nerve and vagal filaments from the left side enter the former, while all others enter the deep

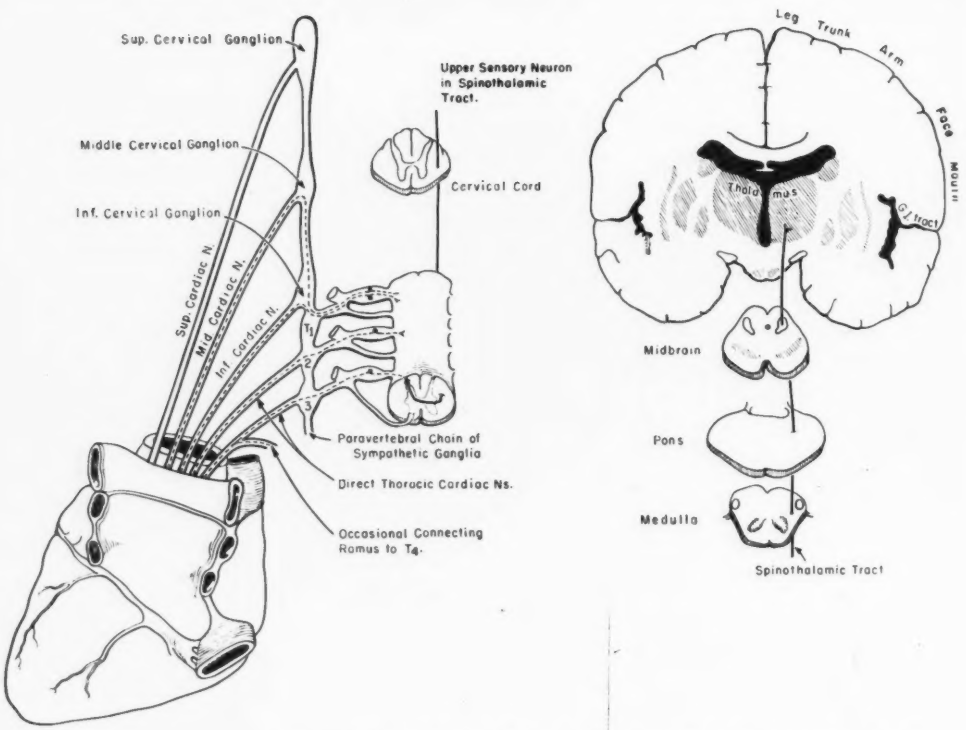

FIG. 2. Diagrammatic representation of the cardiac pain pathways. Pain from coronary insufficiency in the left ventricle tends to follow this course, with a similar arrangement on the opposite side for conduction of pain from the right ventricle. There is no proof that cardiac sensation is propagated above the thalamic level to the cortex.

plexus. This disposition is not a constant one and, as both parts are so interconnected, it is best to consider the cardiac plexus as a single unit. In it the sympathetic and vagal fibers intermingle and lose their identity, but there is a tendency toward a subdivision into right and left halves from which fibers are distributed to the heart along the 2 coronary arteries. Surgical interruption of the superficial portion of the plexus has been advocated for the relief of angina pectoris by Arnulf[13] and pericoronary neurectomy by Fauteux.[14] Both methods have proved capable of relieving pain.

Sympathetic Cardiac Nerves

The anatomic arrangement of the sympathetic cardiac nerves and their central pathways in the spinal cord and brain stem are illustrated in diagrammatic fashion in figure 2. The paravertebral chains of ganglia run on the anterolateral surfaces of the vertebrae on each side of the spinal column from the first cervical down to the lower end of the sacrum. In the thoracic spine there is a ganglion for each vertebra, but the first thoracic is usually attached by an isthmus to the larger inferior cervical ganglion. This dumbbell-shaped structure, which lies in contact with the costovertebral articulation of the first rib, is known as the stellate ganglion. There are only 3 ganglia in the neck. The inferior or upper half of the stellate is connected with the middle cervical ganglion by a number of delicate fascicles that surround the subclavian artery (annulus of Vieussens). The sympathetic chain from this point upward consists of a single well-defined trunk situated behind the carotid sheath on the fascia over the longus colli and

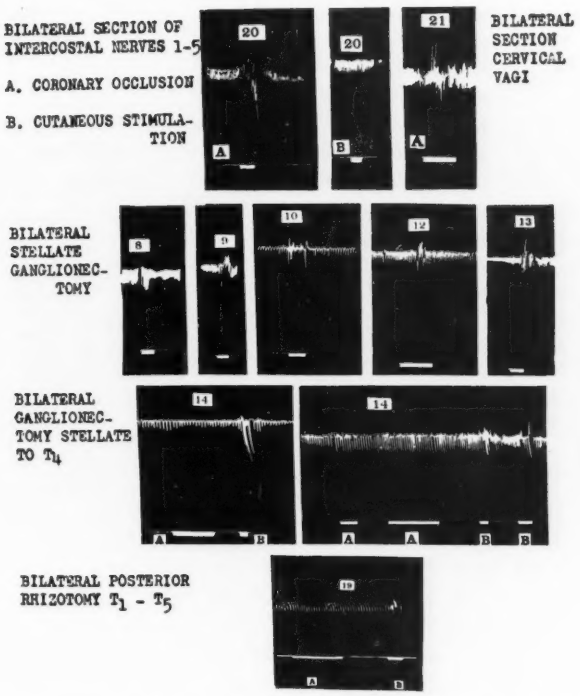

FIG. 3. Sensory denervation of the heart in dogs by White, Garrey, and Atkins.[9] These kymographic tracings are reproduced from article by White and Bland,[22] with the kind permission of the publisher, Williams and Wilkins, Baltimore. After recovery from the preliminary neurosurgical procedure the effectiveness of denervation was tested by Sutton and Lueth's[4] method of interruption of blood flow in the descending branch of the left coronary artery. Changes in respiration in upper tracing denote persistence of cardiac pain. The signals in lower tracings represent periods of stimulation.

capitis muscles. Anterior to the second and third cervical vertebrae it broadens into a long fusiform superior cervical ganglion.

The white communicant rami, that carry cardiac accelerator and other autonomic as well as sensory fibers, join each of the upper 3 or 4 thoracic spinal nerves with the corresponding paravertebral ganglia. They are not found in the cervical portion of the sympathetic trunks. The gray rami, which carry postganglionic sympathetic fibers from the ganglia back to the spinal nerves, are present in the cervical as well as lower portions of the ganglionated chains. These distribute efferent sympathetic impulses to the blood vessels, glands, and smooth muscle of the upper extremity, trunk, and head. In the past it has been taught that all sensory fibers run in the white rami. This is not always true, as White and Sweet[15] have evoked pain on stimulation of gray as well as white rami in conscious patients on the operating table. Nevertheless, as will be made clear below, there is no reason to assume that there are any sensory pathways of clinical significance between the heart and spinal cord above the first thoracic spinal nerve.

In addition to the communicant rami between the sympathetic chains and the spinal nerves, the cervical and upper thoracic ganglia give off visceral rami to the heart. The superior, middle, and inferior cardiac nerves, which arise from the corresponding ganglia, have long been known and were clearly illustrated in a superb plate by Lancisius published in 1728. With the possible exception of the superior, all contain sensory as well as sympathetic motor axons.

The thoracic cardiac nerves, accessory connections of variable importance, were first described in 1830 by Swan,[16] but then entirely forgotten. They were rediscovered by the anatomists less than 30 years ago.[17-19] These delicate rami are given off in a variable fashion from the second down to the third or fourth thoracic ganglia. Their demonstration by careful anatomic dissection did not necessarily imply that they were important accessory pathways in the transmission of cardiac pain. This, however, seemed to be a likely possibility in view of the frequent failure of cervical sympathectomy to relieve angina pectoris.

The transmission of pain over these structures was tested in dogs (fig. 3) by White, Garrey, and Atkins.[9] The stimulus used to induce pain was Sutton and Lueth's[4] method of temporary occlusion of the posterior descending branch of the left coronary artery. This procedure invariably evoked evidence of definite discomfort in control dogs. In others, in which various types of denervation had been previously carried out, it was clearly demonstrated that: (1) bilateral vagotomy does not reduce pain after coronary occlusion; (2) bilateral resection of the stellate ganglia may reduce, but certainly does not eliminate pain after coronary occlusion; (3) after resection of the stellate and upper 4 thoracic ganglia no pain can be evoked; (4) after bilateral section of the upper 4 thoracic posterior spinal roots pain cannot be evoked.

This experiment proved, at least for the dog, that there are sensory axons transmitting painful impulses caudal to the cervical cardiac nerves and that all central connections must pass through the upper 3 or 4 thoracic sympathetic ganglia and the posterior roots of the corresponding spinal nerves. Fortunately clinical experience in man has shown that the dog is a reliable experimental animal in this respect, which is far from the case with transmission of pain in the spinal cord. It is now thoroughly established that pain often reaches the spinal cord over the thoracic, as well as the 2 lower cervical cardiac nerves; in these individuals removal of the stellate ganglia or even the entire length of the cervical chains will not relieve angina pectoris as long as the upper 3 thoracic ganglia with their rami are left intact. On the other hand, since painful impulses that reach these structures over the cervical cardiac nerves must descend caudally at least as far as the first thoracic ganglion, removal of the sympathetic chain down to the third or fourth thoracic will relieve pain consistently. Removal of the upper 3 thoracic ganglia is usually sufficient (table 1), but in view of possible more caudal connections (posterior fixation) it is safer to remove the fourth ganglion in addition. When this is done, the chances of subsequent regeneration are lessened as well. Destruction of the sympathetic ganglia in the upper thorax can be carried out either by surgical resection or by paravertebral injection of ethyl alcohol. This latter method is reserved today for only the poorest risk patients with coronary disease. In such individuals, who often cannot tolerate general anesthesia and a major neurosurgical operation, chemical destruction of these focal ganglia is a most valuable substitute (table 2).

TABLE 1.—*Results of Thoracic Ganglionectomy in Intractable Angina Pectoris*

	No. of cases	Per cent
Total personal cases	17	
Complete relief of precordial and arm pain on denervated side	13	77
Residual slight pain in neck and jaw	2	
Late partial recurrence	3	
Early failure (incomplete denervation)	1	6
Hospital deaths	3	18

Alternative methods of interrupting the peripheral autonomic fibers to the heart have been proposed by Fauteux[14] and Arnulf.[13] These consist of resecting short portions of the pericoronary nerves or the pre-aortic plexus through an anterior thoracotomy. These procedures interrupt vagal and sympathetic motor as well as their accompanying sensory fibers. Both seem illogical. Opening the pleura and operating on the exposed heart must involve more trauma than either extrapleural sympathectomy or section of posterior spinal roots. It is always more difficult to be sure of removing all the finer sympathetic rami in their

TABLE 2.—*Results of Paravertebral Block with Alcohol in Intractable Angina Pectoris*

	No. of cases	Per cent
Total personal cases	77	
Complete relief (later partial recurrence in 14 after intervals of 2½ mos. to 5 yrs.)	43	56
Unclassified (excellent early result, but inadequate follow-up)	5	7
Worthwhile improvement	16	21
Failure	6	8
Died in hospital	7	9

TABLE 3.—*Results of Posterior Rhizotomy in Intractable Angina Pectoris*

	No. of cases	Per cent
Total personal cases	2	
Complete relief to death at 2½ yrs.	1	50
Failure (probably because the 1st thoracic root was not cut)	1	50
Cases reported from other clinics	30	
Complete relief on operated side	26	87
Slight residual pain	1	3
Deaths	3	10

peripheral plexuses than the well-defined paravertebral chains. A final consideration is the notorious proclivity of sympathetic axons to regenerate over short gaps. Patients so far reported have not been followed over sufficiently long periods to exclude this possible cause for recurrent anginal attacks.

Posterior Spinal Roots

When in-coming sensory axons from either the cervical or thoracic cardiac nerves have passed through the upper thoracic sympathetic ganglia they continue over the rami communicantes to reach the corresponding spinal nerves. After a short course within the intervertebral foramina they enter the posterior roots with other sensory axons. These come from the deeper tissues and skin over the medial surface of the arms and chest from the clavicles down to the level of the nipples. The cells of these sensory axons are situated in the posterior root ganglia, and their peripheral fibers differ from the efferent sympathetic preganglionic and postganglionic fibers in running nonstop without synapses through the paravertebral ganglia to the heart. Their central processes terminate in the posterior horn of gray matter, where they establish synapses with nerve cells of the secondary sensory neurons that run in the spinothalamic tracts. There is evidence, cited by Ruch,[20] that there are insufficient secondary sensory fibers to supply all the in-coming primary pain fibers in the posterior roots. Therefore it is probable that visceral and somatic impulses often share a single pain fiber in the spinothalamic tract. In view of this arrangement it is easy to see why cardiac pain is referred by the sensorium to the precordial region and inner surface of the arms.

In planning a neurosurgical procedure for relief of cardiac pain, posterior rhizotomy is the best if the patient's coronary circulation is adequate to permit an operation of this extent. In 32 patients, summarized in table 3, it has been successful in all but a single case. Failure in this instance, one of my own patients, can be ascribed to a technical error, as I failed to sever the important first posterior root. It is of vital importance to localize the first thoracic vertebra by an x-ray taken on the operating table and to remove all but the uppermost portion of its lamina. The roots from this first thoracic segment leave the cord at the lower border of the seventh cervical vertebra and pass through the dura at so high a level that they will not be seen unless a considerable portion of the uppermost thoracic lamina has been removed. After division of the posterior sensory roots regeneration is impossible and postoperative pain, which may be an annoying complication after resection of the sympathetic ganglia, as well as after paravertebral injection, is never a problem. In addition, bilateral denervation can be carried out at a single stage.

Central Conduction of Cardiac Pain in the Spinal Cord

The secondary sensory axons, whose neuron cells lie in the posterior horn, soon decussate and cross in the anterior commissure to the spinothalamic tract in the opposite anterior quadrant. Figure 2 illustrates their rostral

course through the brain stem to the posteroventral nucleus of the thalamus. While no observations on the effect of high cervical cordotomy have been reported in cases of angina pectoris, it is probable that this operation would interrupt pain provided analgesia were complete to the lower level of the brachial plexus. In other varieties of visceral disease unilateral transection of the spinal pain pathway has interrupted pain from the biliary tracts, kidney, and intestine on the contralateral analgesic side.[15] When the pain has been felt on both sides, as in intestinal obstruction, it has not been reduced on the ipsilateral side in which sensibility has remained intact. Cordotomy, however, is never necessary in cases of cardiac pain, as sympathetic denervation or posterior rhizotomy are more simple and innocuous procedures.

Perception of Cardiac Pain in the Thalamus and Cerebral Cortex

Pain-conducting fibers in the spinothalamic tracts terminate in the posterolateral and ventral nuclei of the thalamus (fig. 2). While more refined modalities of sensation from the surface of the body are carried upward to the postcentral cortex, it is doubtful if this occurs to any notable extent in perception of pain. The sensory cortex doubtless is the means whereby cutaneous pain is localized, but this ability is not developed for the viscera. In a number of total removals of a hemisphere that I have recently studied, the disagreeable quality of pain on the opposite side of the body has not been diminished, although the ability to localize accurately the point pricked, especially in the extremities, has been markedly reduced. On the other hand, when the thalamus has been destroyed by an abscess or tumor, all contralateral perception of pain has been abolished. While cardiac pain cannot be experimentally produced in man, I hope soon to test the extent to which pain on distention of the contralateral renal pelvis is altered after hemispherectomy. I doubt that it will be altered in any significant way.

In terminating this section on anatomy of the sensory innervation of the heart it seems appropriate to emphasize its therapeutic value. The effectiveness of interrupting the pathway either in the spinal roots or in the paravertebral sympathetic ganglia has been summarized in tables 1, 2, and 3.

It will be seen from a study of these data that failure to relieve precordial pain and arm radiation is extremely rare when it is certain that the known afferent pathways to the heart have been interrupted. After excision of the central end of the second rib complete resection of the first and third ganglia with their rami is often difficult. Similarly, when the anterior supraclavicular approach is used, exposure of the third ganglion is not always easy. At times pain-conducting fibers must pass through the fourth thoracic ganglion below as well. In performing a rhizotomy the surgeon, to be certain of cutting the important first thoracic posterior root, must remove nearly the entire lamina of the corresponding vertebra, as I have found to my chagrin in investigating a case that failed. Failures are of course more frequent after attempts to interrupt pain conduction through the sympathetic ganglia and their rami by chemical block with ethyl alcohol. In this group I have seen no failures provided the injection resulted in a Horner's sign and hot, dry arm indicative of effective interruption of the regional sympathetic vasoconstrictor and sudomotor outflow.

In selecting the method of denervation for a given patient it is best to be guided by the degree of cardiac reserve. Patients who have had recent coronary thrombosis, the sufferers from angina decubitus, or those who have aortic regurgitation and are threatened with cardiac failure are not proper risks for any major surgical procedure. With experience in paravertebral block it is possible to treat these patients by injecting alcohol with a reasonable chance of success and fair degree of safety. Section of the posterior sensory roots is undoubtedly the surest method of securing permanent relief, because regeneration of sensory as well as sympathetic fibers is occasionally seen after ganglionectomy, as well as after chemical blocking.

The apparent higher rate of mortality in my 17 ganglionectomies (18 per cent), as compared to the figure of 10 per cent after 30 rhizotomies,

is not of significance in this small series. It amounted to only 7.6 per cent in Olivecrona's larger series reported by Lindgren.[21] If anginal attacks are purely unilateral, it should be somewhat safer to do a sympathetic denervation than a laminectomy. On the other hand, when pain radiates to both arms, rhizotomy, which can be carried out bilaterally, is undoubtedly a safer procedure than a 2-stage ganglionectomy. Rhizotomy carries the lowest risk of disagreeable postoperative complications. After injection of alcohol pneumothorax is an occasional but not serious complication. Intercostal neuralgia is more frequently troublesome, but this has lasted for prolonged periods in only 10 per cent of our cases and never for longer than 3 months. Postoperative discomfort has been equally troublesome in the patients after resection of the ganglia.

In following the surgically treated patients, particularly those who are having such frequent attacks of angina decubitus that they are in fear of imminent death and unable to rest, the results have been particularly gratifying. A number of my patients, rescued from the intolerable pain of frequent severe nocturnal attacks, are reported in detail in published accounts with Bland,[22] with Smithwick and Simeone[23] and with Sweet.[15] Many recovered to regain a useful degree of activity and continued to live in comfort for long periods. One is alive, free of angina, and leading a moderately active life at 85, 19 years after her paravertebral injection. It would appear that sensory denervation of the heart, when medical methods fail, may prolong life by reducing pressor responses that accompany severe pain and prevent relaxation by day and sleep at night. Giving the patient a reprieve from suffering is often an effective method for promoting the spontaneous recovery of a more adequate coronary circulation.

Physiologic Mechanisms

Pain experienced in an attack of angina pectoris is felt characteristically beneath the sternum and down the inner surfaces of one or both arms, and at times in the little and ring fingers as well. Occasionally it may be referred to the neck or jaws. The typical area of reference is supplied by the first to fourth thoracic spinal nerves. As mentioned above, it has long been known that there are no white rami communicantes connecting the paravertebral ganglia with the spinal cord in the cervical region and that the thoracolumbar sympathetic motor outflow begins at the first thoracic spinal segment. It would appear that this must apply to afferent sensory, as well as sympathetic motor fibers, as cardiac pain is invariably relieved by cutting the upper 4 thoracic sensory spinal roots. When pain is referred to both arms, sensory denervation, either by dividing these posterior roots or by destroying the corresponding paravertebral sympathetic ganglia, must be carried out on both sides. On the other hand, when the arm on only one side is involved, pain is eliminated by a unilateral denervation. While attacks of unilateral angina usually radiate to the left arm, 7 of my 96 patients had purely right-sided involvement, and good results followed a right-sided operation in these cases.

The mechanism of pain occasionally felt in the neck and jaws is still not understood. A complete resection of the cervical sympathetic chain with removal of its superior, middle, and inferior ganglia had no effect whatever in relieving 1 of my patients with residual angina in the left side of the neck and lower jaw, after all pain in the precordium and arm had been controlled by removal of the upper thoracic sympathetic ganglia. Lindgren and Olivecrona [21, 24] subsequently reported that pain referred to the jaws can be interrupted by alcohol block of the mandibular or maxillary nerves.

James Mackenzie, who wrote so extensively about angina pectoris over a period of 30 years, summarized his ideas in his final monograph in 1924.[25] He emphasized 2 points about cardiac pain, both of which have been proved incorrect in recent years. In the first place, he claimed that surgical relief of cardiac pain would endanger the patient's life because angina was an important warning signal of overexertion. This is fortunately not the case, because even after bilateral sensory denervation the patient continues to experience an adequate warning signal, even though he is completely spared from his former agonizing attacks. Painless equivalents persist as a sense of constriction in

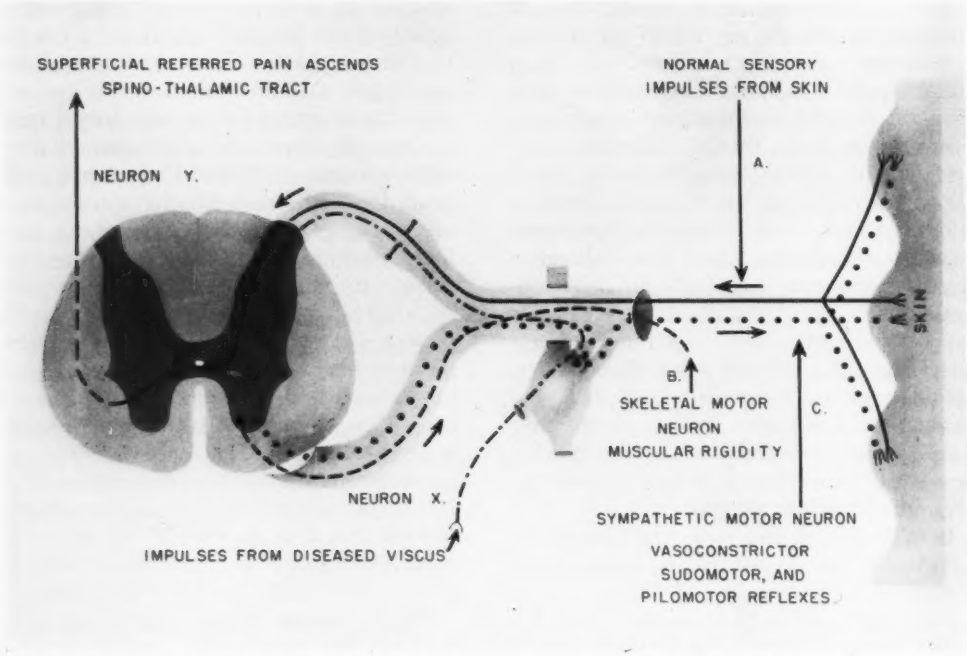

FIG. 4. The viscerocutaneous reflex of Mackenzie. Reproduced from White and Sweet,[15] with the kind permission of the publisher, Charles C Thomas, Springfield, Ill. Mackenzie[25] hypothesized that sensory impulses from the heart end with neuron X in the posterior spinal horn of gray matter. Here, during attacks of visceral pain, an irritable focus is set up, which permits normally subthreshold cutaneous impulses to cross the synapse and fire off the cell of the spinothalamic neuron. If this were the sole mechanism, pain should not be felt after cutaneous block with procaine nor in a phantom arm after shoulder amputation.

the suprasternal notch, often accompanied by dyspnea and palpitation.

Mackenzie also thought that there were no spinal pathways for cardiac or other forms of visceral pain. He popularized the theory that all visceral pain was referred to the surface of the body in characteristic areas by means of a viscerocutaneous reflex. As illustrated in figure 4, he believed that painful discharges from a diseased organ travel centrally only as far as the posterior horn of gray matter in the spinal cord. He then assumed that there were no specific secondary neurons to conduct pain upward in the spinothalamic tract. According to Mackenzie's theory, cardiac pain, on reaching the posterior horn, sets up an irritable focus, which reduces synaptic resistance to such an extent that sensory stimuli from corresponding cutaneous dermatomes, ordinarily of subthreshold intensity, continue upward in the spinothalamic tract to reach the level of consciousness. This theory of cutaneous reference of visceral pain was adopted by Mackenzie from the previous writings of James Ross[26] and Henry Head.[27] Both these men, however, believed that there was also direct conduction of splanchnic pain, poorly localized in the midline. It is a pity that Mackenzie abandoned this concept and, through his prestige and frequent writings, confused this issue for nearly 50 years.

The theory of referred pain, although still a possible mechanism, must play a very minor role. Sir Thomas Lewis, in his monograph on *Pain*,[28] stated that infiltration of procaine over the entire precordial area "failed to alter, in the least, anginal pain in an eminently suitable patient in whom the referred pain was focused

over the sternum and could be provoked, with regularity and by a constant amount of effort, both before and after thoroughly anaesthetising the affected part of the body wall." Cohen[29] reported the pertinent observation that 2 of his patients with high amputations of the arm developed angina pectoris with reference of pain to the phantom extremity. In other varieties of visceral pain a number of clear-cut observations prove that the sensation may persist with little or no alteration when all afferent impulses from the surface areas to which the pain is referred have been blocked.[30]

It is therefore evident that pain from the heart and other viscera cannot be interrupted by any form of cutaneous denervation distal to the point of inflow of the sympathetic rami communicantes, over which visceral afferent impulses enter the posterior horn of the spinal cord.

There are good reasons why cardiac and other forms of visceral pain are localized so poorly. In the first place, all deep structures, not only the internal organs, but also skeletal muscle, fascia, and ligaments have very few painful nerve endings. The ability to localize pain, so accurately possessed by the skin and oral mucosa, is due to their rich supply of sensory endings. Of the deeper structures only periosteum has a sufficient supply to localize the source of painful stimuli with fair accuracy. The viscera differ in this respect in no way from skeletal muscle and ligaments, as Lewis[28] showed in his experiments on himself and other workers in his laboratory. Injection of hypertonic salt solution in the upper thoracic interspinous ligaments was indistinguishable from cardiac pain. On injection of the fascia overlying the rectus abdominis muscle the discomfort evoked resembled an attack of abdominal colic. Furthermore, as Ruch[20] has pointed out, the number of pain fibers in the spinothalamic tract is far less than the number entering the posterior sensory roots. This means that many primary visceral and cutaneous afferent neurons must share the same secondary spinothalamic fibers in order to reach the thalamus and sensorium. As a result, the individual will refer painful impulses from the viscera to the area of more commonly experienced cutaneous sensation. It is therefore not surprising that visceral pain is referred to certain characteristic superficial areas that are innervated from corresponding levels of the spinal cord.

In the case of the heart the dermatomal distribution of the first and second thoracic nerves includes the inner surface of the arm and forearm together with the hypothenar eminence and a variable portion of the little and ring fingers; the anterior divisions of the second, third, and fourth intercostal nerves innervate the precordial region above the nipple line. On stimulation of the stellate and second thoracic sympathetic ganglia in the course of operations under local anesthesia by my colleague, Dr. William H. Sweet, and myself, a number of patients have complained of pain difficult to localize in the upper thorax and occasionally radiating down the arm. The sensation evoked, however, has not resembled an attack of angina pectoris.

Why pain in angina pectoris is referred only to the anterior chest wall and skips the lateral and posterior divisions of the intercostal nerves is not known. This is true of many forms of pain from the abdominal viscera as well. Only pancreatic and renal pain are commonly felt in the back as well as in the abdominal wall. There is also no adequate explanation for the sense of constriction in the suprasternal notch that persists after complete interruption of the sympathetic cardiac pain fibers. It is possible that this sensation is transmitted by vagal fibers and also that some form of vago-trigeminal reflex mechanism may account for the pain that is occasionally referred to the jaws; yet no pain of any sort was experienced by a patient in whom I observed Leriche stimulate the exposed vagus in the course of a resection of the stellate ganglion under local anesthesia.

Summary

It may be concluded that the pathways of cardiac pain have been thoroughly established, with the exception of the conduction of anginal attacks occasionally referred to the neck and jaws. Afferent impulses traverse axons that travel in the cervical and thoracic sympathetic cardiac nerves. In the case of the cervical pathway, all impulses on entering the paravertebral

ganglionated chain in the neck must descend to the upper thoracic level before they can gain access to the spinal cord. Other impulses reach the 3 superior thoracic ganglia via the more direct thoracic cardiac nerves. Both the cervical and thoracic fibers join the spinal nerves over the communicant sympathetic rami. After passing through the intervertebral foramina, they enter the posterior roots and terminate in the lateral horn of the spinal cord. Here they establish synapses with secondary afferent neurons of the spinothalamic tract, decussate to the opposite anterior column, and are carried rostrally to the nucleus ventralis posterolateralis of the thalamus. This is the principal locus in the brain for the perception of visceral pain. In contrast to well-defined cutaneous sensibility, there is no cortical area for exact visceral localization in the postcentral region of the cerebral cortex.

Another factor in the poor localization of cardiac pain is the paucity of sensory endings in the heart. A third appears to be the limited number of secondary sensory fibers in the spinothalamic tracts. These central axons must be shared with other impulses from the surface of the body. As a result, pain from the heart is in large part referred to the cutaneous distribution of the upper 4 thoracic spinal segments. Accounting for the superficial reference of visceral pain by Mackenzie's theory of a viscerocutaneous reflex is no longer justifiable. Even after cutaneous afferent fibers are interrupted by procaine or amputation of the arm, pain from the heart can still be felt over its previous distribution.

Neither stimulation of the vagi nor interruption of transmission in these nerves has been found to have any beneficial effect in patients suffering from angina pectoris. Sensory denervation of the heart must therefore be carried out by destruction of the upper ganglia in the thoracic sympathetic trunks or by severing the corresponding posterior spinal roots.

Summario in Interlingua

Il es permissibile asserer que le vias de transmission de dolores cardiac ha essite precisemente establite, con le exception del conduction de attaccos de angina que se refere a vices al collo e al maxillas. Impulsos afferente transversa axones que viagia in le cervical e thoracic nervos cardiac sympathic. In le caso del via cervical, omne impulsos que ha entrate in le catena ganglionate paravertebral in le collo debe descender al nivello supero-thoracic ante que illos pote obtener accesso el medulla spinal. Altere impulsos attinge le 3 gangliones supero-thoracic plus directemente via le nervos cardiac thoracic. Le fibras cervical e thoracic se junge ambes con le nervos spinal supra le communicante ramos sympathic. Post passar per le foramines intervertebral, illos entra in le radices posterior e se termina in le corno lateral del medulla spinal. Hic illos establi synapses con afferente neurones secundari del tracto spinothalamic, decussa al opposite columna anterior e es portate rostralmente al nucleo ventral posterolateral del thalamo. Isto es le loco principal del cerebro pro le perception de dolores visceral. In contrasto con le ben-definite sensibilitate cutanee, il non existe un area cortical pro le exacte localisation visceral in le region postcentral del cortice cerebral.

Un altere factor in le pauco precise localisation de dolores cardiac es le paucitate de terminationes sensori in le corde. Un tertie factor es apparentemente le restringite numero de secundari fibras sensori in le tractos spinothalamic. Iste axones central debe etiam servir altere impulsos ab le superficie del corpore. Le consequentia es que dolores in le corde es in grande parte referite al distribution cutanee del 4 superior segmentos spinal thoracic. Explicar le referentia superficial de dolores visceral per medio del theoria de Mackenzie de un reflexo viscero-cutanee ha perdite omne justification. Mesmo post que fibras afferente cutanee es interrumpite per procaina o per amputation del bracio, dolor ab le corde pote ancora sentir se in su previe distribution.

Ni le stimulation del nervos vage ni le interruption del transmission in iste nervos ha potite exercer un effecto benefic in patientes quisuffre de angina de pectore. Disnervation sensori del corde debe per consequente esser executate per medio del destruction del gangliones superior in le truncos sympathic thoracic o per dissecar le correspondente radices spinal posterior.

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BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed

Proceedings of the Annual Meeting. Council for High Blood Pressure Research, American Heart Association, Cleveland, Ohio, Nov. 18–19, 1955. Vol. IV. New York, American Heart Association, 1956, 186 pages. $4.50.

Die Röntgen-Untersuchung des Herzens und der Grossen Gefässe. *R. Janker, F. Grosse-Brockhoff, R. Haubrich, H. Lotzkes, A. Schaede, and H. Hallerbach.* Wuppertal-Elberfeld, Germany, W. Girardet, 1956, 222 pages.

Röntgenologische Funktionsdiagnostik. Mittels Serienaufnahmen und Kinematographie. *Robert Janker.* 2 volumes. Bonn, W. Girardet, 1956. DM 39.

Radiology of the Heart and Great Vessels. *Robert N. Cooley and Robert D. Sloan.* Baltimore, Williams and Wilkins Co., 1956, 309 pages, 195 figures. $12.00.

Les angors coronariens intriqués. Étude clinique et expérimentale des inter-réactions neuro et viscéro-coronariennes. *Roger Froment and André Gonin,* with the collaboration of *P. Bruel and R. Mornex.* Paris, Expansion Scientifique Francaise, 1956, 173 pages, 33 figures.

Handbook of Differential Diagnosis. Ed. 2. *Harold Thomas Hyman.* Philadelphia, J. B. Lippincott Co., 801 pages, 1956. $9.00.

Handbook of Biological Data. Edited by *William S. Spector.* Division of Biology and Agriculture, The National Academy of Sciences, The National Research Council. Technical Report No. 56-273, 1956, 584 pages. $7.50.

Paper Electrophoresis. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme and Elaine C. P. Millar.* Boston, Little, Brown and Company, 1956, 224 pages, 74 illustrations. $6.75.

Bone Structure and Metabolism. Ciba Foundation Symposium. Edited by *G. E. W. Wolstenholme and Cecilia M. O'Connor.* Boston, Little, Brown and Company, 1956, 299 pages, 121 illustrations. $8.00.

Verhandlungen der Deutschen Gesellschaft fur Kreislaufforschung. Thema: Korrelationen zwischen Herz und Gefäbsystem. Edited by *Rudolf Thauer.* Darmstadt, Dietrich Steinkopff, 1956, 374 pages, 140 illustrations. DM 48.

Clues in the Diagnosis and Treatment of Heart Disease. Ed. 2. *Paul. D. White.* Springfield, Illinois, Charles C Thomas, 1956, 190 pages, 40 figures. $5.50.

Low-Fat Cookery. *Evelyn S. Stead and Gloria K. Warren.* New York, McGraw-Hill Book Company, Inc., 1956, 184 pages. $3.95.

Pulmonary Circulation and Respiratory Function. A Symposium. Queen's College, University of St. Andrews. Edinburgh and London, E. and S. Livingstone, Ltd., 1956, 44 pages. $2.00. (Available through The Williams and Wilkins Company, Baltimore, Md.)

Cardiopathies congénitales. Ed. 2. *P. Soulié.* Paris, Expansion Scientifique Francaise, 1956, 448 pages, 369 illustrations.

Diabetes Mellitus. Handbook for Physicians. *Howard F. Root and Priscilla White.* New York, McGraw-Hill Book Company, Inc., 1956, 346 pages. $7.00.

Diseases of the Heart. Ed. 2. *Charles K. Friedberg.* Philadelphia, W. B. Saunders Company, 1956, 1161 pages, 157 figures. $18.00.

World Trends in Cardiology. Five Volumes: I. Cardiovascular Epidemiology. Edited by *Ancel Keys and Paul D. White,* 102 pages. $4.75. **II. Cardiovascular Surgery.** Edited by *Helen B. Taussig and Arthur S. Cain, Jr.* 65 pages. $2.00. **III. Blood Volume and Contractile Protein in Heart Muscle.** Edited by *Arthur S. Cain, Jr.* 131 pages, $3.50. **IV. Cardiovascular Diagnosis and Therapy.** Edited by *Arthur S. Cain, Jr.* 95 pages. $3.85. **V. Instrumental Methods in Cardiac Diagnosis.** Edited by *Louis N. Katz and Arthur S. Cain, Jr.* 100 pages. $3.85. New York, Paul B. Hoeber, Inc., 1956.

Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology. *Robert E. Woodson, Jr., Heber W. Youngken, Emil Schlittler, and Jurg A. Schneider.* Boston, Little, Brown and Company, 1956, 149 pages, illustrated. $5.50.

La balistocardiographie (valeur pratique). *J. Desruelles and J. F. Merlen.* Paris, Expansion Scientifique Francaise, 1957, 208 pages, 108 figures. 2.200 fr.

La cardiopéricardiomyopexie. Diagnostic et nouveau traitement chirurgical de l'angine de poitrine et des cardiopathies rhumatismales. *Camille Lian, A. N. Gorelik, and Mendel Jacobi.* Paris, Expansion Scientifique Francaise, 1956, 104 pages, 26 figures. 900 fr.

L'année cardiologique internationale. *Camille Lian.* Paris, Expansion Scientifique Francaise, 1956, 374 pages, 116 figures. 2.200 fr.

Liver: Structure and Function. *Hans Popper and Fenton Schaffner.* New York, McGraw-Hill Book Company, Inc. 1956, 777 pages, 204 figures. $20.00.

Les troubles trophiques des membres inférieurs

d'origine veineus. *Jacques Charpy and M. Audier.* Paris, Masson et Cie, 1956, 376 pages, 156 figures. 2.500 fr.

Physical Basis of Ballistocardiography. *Abraham Noordergraaf.* 'S-Gravenhage, Netherlands, Uitgeverij Excelsior, 1956, 146 pages.

Hypotensive Drugs. Edited by *M. Harington.* New York, Pergamon Press, 1956, 221 pages. $8.00.

Synopsis of Pathology. Ed. 4. *W. A. D. Anderson.* St. Louis, C. V. Mosby Co., 1957, 829 pages, 328 figures, 12 color plates. $8.75.

The Merck Manual of Diagnosis and Therapy. Ed. 9. Rahway, N. J., Merck and Co., Inc., 1956, 1870 pages. $6.75.

The Physician-Writer's Book. Tricks of the Trade of Medical Writing. *Richard M. Hewitt.* Philadelphia, W. B. Saunders Company, 1957, 415 pages. $9.00.

Pediatric Cardiology. *Alexander S. Nadas.* Philadelphia, W. B. Saunders Company, 1957, 587 pages 343 figures. $12.00.

Clinical Unipolar Electrocardiography. Ed. 3. *Bernard S. Lipman and Edward Massie.* Chicago, The Year Book Publishers, Inc., 1956, 397 pages, 325 figures. $7.50.

The Importance of Overweight. *Hilde Bruch.* New York, W. W. Norton and Company, Inc., 1957, 438 pages. $5.95.

The Clinical Management of Varicose Veins. Ed. 2. *David Woolfolk Barrow.* New York, Paul B. Hoeber, Inc., 1957, 169 pages, 70 figures. $6.00.

Coronary Heart Disease: Angina Pectoris; Myocardial Infarction. *Milton Plotz.* New York, Paul B. Hoeber, Inc., 1957, 353 pages, 107 figures. $12.00.

Clinical Use of Radioisotopes. *William H. Beierwaltes, Philip C. Johnson, and Arthur J. Solari.* Philadelphia, W. B. Saunders Company, 1957, 456 pages, 126 figures. $11.50.

Fonocardiografie. Betekenis voor de diagnostiek van enige aangeboren en verworven hartgebreken. *J. W. Gerritsen.* Groningen, Boekdrukkerij Voorheen Gebroeders Hoitsema, 1957, 117 pages, 45 figures.

The Happy Life of a Doctor. *Roger I. Lee.* Boston, Little, Brown and Company, 1957, 276 pages. $4.00.

Diseases of the Heart and Circulation. Ed. 2. *Paul Wood.* Philadelphia, J. B. Lippincott Company, 1956, 1005 pages, illustrated. $15.00.

The Early Detection and Prevention of Disease. Edited by *John P. Hubbard.* New York, McGraw-Hill Book Company, Inc., 1957, 350 pages. $7.50.

Radicular Syndromes. With emphasis on chest pain simulating coronary disease. *David Davis.* Chicago, The Year Book Publishers, Inc., 1957, 266 pages, 69 illustrations. $6.50.

Principles of Urology. An introductory textbook to the diseases of the urogenital tract. *Meredith F. Campbell.* Philadelphia, W. B. Saunders Company, 1957, 622 pages, 319 figures. $9.50.

Guide to Medical Writing. *Henry A. Davidson.* New York, The Ronald Press Company, 1957, 338 pages. $5.00.

I^er^ Symposium de la Fondation Valentino Baldacci. Hémostase spontanée, plaquettes sanguines et parois vasculaires. Pisa, Italy, Omnia Medica, 1956, 190 pages.

Expectant Motherhood. Ed. 3. *Nicholson J. Eastman.* Boston, Little, and Company, 1957, 198 pages. $1.75.

Clinical Physiology. The functional pathology of disease. Edited by *Arthur Grollman.* New York, McGraw-Hill Book Company, Inc., 1957, 854 pages. $12.50.

The Venous Pressure in the Pulmonary Circulation. Measured by the indirect method during cardiac catheterization. *Asger Pedersen.* Copenhagen, Arnold Busck, 1956, 286 pages.

Clinical Cardiopulmonary Physiology. Sponsored by the American College of Chest Physicians. *Burgess L. Gordon, Editor-in-Chief.* New York, Grune and Stratton, Inc., 1957, 768 pages, 248 illustrations, 32 tables. $15.75.

Clinical Electrocardiography. Interpretation on a physiologic basis. *Manuel Gardberg.* New York, Paul B. Hoeber, Inc., 1957, 315 pages, 259 illustrations. $12.75.

Atlas of Clinical Endocrinology. *H. Lisser and Roberto F. Escamilla.* St. Louis, C. V. Mosby Co., 1957, 476 pages, 148 plates including 3 in color. $18.75.

Der ultramikroskopische Bau von Herz und Kapillaren. *Bruno Kisch.* Darmstadt, Dietrich Steinkopff, 1957, 109 pages, 75 figures. DM 25.

Hypothermie et Chirurgie Cardiaque. *Yannik Le Corroller.* Paris, Librairie Maloine, 1956, 143 pages, 19 figures. 800 fr.

Insuffisance Cardiaque. *J. Lo Jacomo.* Paris, Librairie Maloine, 1957, 392 pages, 37 figures, 9 microphotographs. 1.000 fr.

Human Blood Groups and Inheritance. *Sylvia D. Lawler and L. J. Lawler.* 103 pages. Boston, Cambridge, Harvard University Press, 1957, 103 pages. $1.50.

ABSTRACTS

ATHEROSCLEROSIS

Blankenhorn, D. H., Freiman, D. G., and Knowles, H. C., Jr.: Carotenoids in Man. The Distribution of Epiphasic Carotenoids in Atherosclerotic Lesions. J. Clin. Invest. **35:** 1243 (Nov.), 1956.

Carotenoid pigments are colored lipids distributed widely throughout nature. Certain carotenoids, chiefly those without hydroxyl groups, can be converted to vitamin A. Studies have indicated that carotenoids cannot be synthesized by man. It was thought advisable, therefore, to study the occurrence of these lipids in atheromatous plaques, as evidence that dietary lipid may be deposited in the lesions. The concentrations of total carotenoids and total cholesterol were studied in 30 human aortas with varying degrees of atherosclerosis. With increase in the severity of the lesions, there were accompanying significant increases in carotenoid and cholesterol contents. The carotenoid-cholesterol ratio was relatively constant. Although cholesterol in the plaque may accumulate either inside the plaque or outside, it is generally accepted that carotenoids are derived from exogenous sources. Although it is unknown whether carotenoid pigments are concerned with the pathogenesis of atherosclerotic lesions, the present findings give evidence that one dietary lipid is present not only in atherosclerotic plaques but accumulates in direct proportion to age and extent of the lesions.

WAIFE

Adlersberg, D., Schaefer, L. E., Steinberg, A. G., and Wang C-I.: Age, Sex, Serum Lipids, and Coronary Atherosclerosis. J.A.M.A. **162:** 619 (Oct. 13), 1956.

Twelve hundred healthy males and females in Staten Island (New York) between the ages of 2 and 17 were examined and their sera analyzed for cholesterol and phospholipids to determine the average lipid levels for this population. Cholesterol and phospholipid levels for men remain constant to age 19, increase from age 20 through 33, and then remain constant to age 60. Levels for women remain constant through age 32 and increase sharply and continuously from age 33 through 58. The difference in the age trends between men and women may perhaps be related to the well-known preponderance of men with coronary artery disease in the younger decades and the proportionate increase in women with coronary atherosclerosis after the age of 50. It is interesting to note that the period of marked increase of serum lipid levels that occurs physiologically in both sexes starts 13 years later in women than in men and lasts 12 years longer.

KITCHELL

Rossi, B., and Rulli, V.: The Hypocholesterolemic Effect of Phenylethylacetic Acid Amide in Hypercholesterolemic Atherosclerotic Patients. Am. Heart J. **53:** 277 (Feb.), 1957.

Fourteen patients with atherosclerosis and pronounced hypercholesterolemia were given phenylethylacetic acid amide, 2 Gm. daily for 2 weeks and 3 Gm. daily thereafter for periods of 3 to 10 weeks. In 13 patients, a significant reduction (ranging from 71 to 5 per cent) of plasma cholesterol was found among the 10 patients who received the drug for 8 to 10 weeks, the mean reduction at the end of treatment was 43.3 per cent. The mean plasma cholesterol value dropped to normal for the major part of the period of treatment, and even below normal during the tenth week. One month after the drug was discontinued the cholesterol values had risen to near the initial prestudy levels.

SAGALL

Keys, A., and Anderson, J. T.: Dietary Protein and the Serum Cholesterol Level in Man. Am. J. Clin. Nutrition **5:** 29 (Jan–Feb.), 1957.

The authors report the results of controlled experiments on metabolically normal, physically healthy schizophrenic men in the 32 to 54-year-old age group who were maintained on diets that were constant in calories but differed in their protein content in order to evaluate the influence of dietary protein on the production of lowered blood cholesterol levels. The response of the total serum cholesterol to a change from a low- to a high-fat intake was the same in 1 group of men receiving 83 Gm. of protein daily as in a matched group on the same diet except for the isocaloric substitution of an extra 43 Gm. of skimmed-milk protein for carbohydrate in the diet. Two groups of subjects were maintained on a low-protein intake, were changed for 4 weeks to a high-protein intake and then were changed back to the low-protein intake, all at a constant fat intake. No significant change in the serum cholesterol level was found in either group at any time. Also, an increase of 1,000 mg. per day in the dietary cholesterol intake, maintained for 8 weeks, had no significant effect on the serum cholesterol level.

SAGALL

Rome, S.: Heparin in Senile Macular Degeneration. Arch. Ophth. **57:** 190 (Feb.), 1957.

Twenty-three patients having more or less advanced senile macular degeneration received heparin therapy designed to suppress underlying atherosclerosis. One hundred milligrams of a concentrated aqueous solution was administered intravenously semiweekly in 5- to 10-week periods for as long as 3½ years in an office practice. Seventeen of the 23 improved, while 3 each were stationary or became worse. The disciform type of lesion seemed to respond better than the arteriosclerotic type. No untoward reaction was noted from more than 1,000 heparin injections.

ROGERS

Corazza, L. J., and Myerson, R. M.: Essential Hyperlipemia. Report of Four Cases, with Special Reference to Abdominal Crises. Am. J. Med. **22:** 258 (Feb.), 1957.

Essential hyperlipemia is a clinical state of unknown cause characterized by an increase in the blood neutral fat. Four additional patients are presented, 3 of whom presented initially with pure abdominal pain. Each patient showed a marked increase in blood neutral fat but also increased serum cholesterol, phospholipid, and fatty acids. Moderate impairment of glucose tolerance was demonstrated. On a low-fat diet, symptoms subsided promptly and blood lipid concentrations decreased.

KURLAND

Levkoff, A. H., and Knode, K. T.: The Treatment of Familial Hypercholesterolemia, with a Plant Sterol. Pediatrics **19:** 88 (Jan.), 1957.

Two siblings, aged 11 and 10, who had a very strong family history of hypercholesterolemia were put on a diet, moderately low in cholesterol and were given 20 ml. of a 20 per cent suspension of beta-sitosterol 3 times daily. Measurements were made of the serum cholesterol and serum phospholipids in the individuals at frequent intervals. The initial levels were elevated over the normal. A significant reduction in the concentration of cholesterol in the serum of these individuals was effected by the use of sitosterol administered 3 times daily. Adequate figures are given.

HARVEY

Florsheim, W. H., Morton, M. E., and Goodman, J. R.: The Effect of Thyroid Ablation upon Serum Cholesterol and B-Lipoprotein Spectrum. Am. J. M. Sc. **233:** 16 (Jan.), 1957.

The authors studied the effect of reduction of thyroidal activity upon atherogenesis in patients treated with radioiodine by following Gofman's "atherogenic index" and the total serum cholesterol. Mild rises in both parameters occurred in hyperthyroid patients rendered euthyroid. These involved only minimal added risk of atherogenesis by Gofman's calculations. Similar changes followed therapeutic ablation in euthyroid patients not presenting atherosclerotic heart disease. In atherosclerotic patients greater rises in serum total cholesterol and atherogenic index were sometimes observed. Among the patients with heart disease, radioiodine therapy dramatically relieved two thirds of those with incapacitating anginal pains. However, results in the patient presenting cardiac insufficiency secondary to pulmonary dysfunction and in several other such patients not included in this study have been less favorable. In patients thyroidectomized for cardiac insufficiency resulting from arteriosclerotic heart disease, changes in lipoprotein spectrum did not always parallel changes in total cholesterol and lipoprotein changes were not restricted to the S_f 0-12 class. The excellent results obtained by Blumgart and the authors in rehabilitating patients through the relief of cardiac decompensation, congestive failure and anginal pain certainly seem well worth any added small risk of increased atherogenesis.

HARRIS

Texon, M.: A Hemodynamic Concept of Atherosclerosis, with Particular Reference to Coronary Occlusion. Arch. Int. Med. **99:** 418 (March), 1957.

Hemodynamics has been presented as a primary factor in the development of atherosclerosis. A physical basis for occlusive coronary artery disease is offered. A mechanism is described for intimal ulceration, intramural hemorrhage, and dissecting

hemorrhage occurring as complications during the pathogenesis of atherosclerosis. Atherosclerosis would appear to be a sequel primarily of fluid dynamics applied to the natural conditions in the circulatory system. A clinical and pathologic correlation of cardiac stress is discussed.

BERNSTEIN

Bell, H. V.: Fatal Atherosclerotic Encephalomalacia in a Young Man. Arch. Int. Med. **99:** 481 (March), 1957.

Hemorrhage into an isolated atherosclerotic lesion of the right middle cerebral artery was found at autopsy to be the cause of encephalomalacia in a 28-year-old laborer. The remaining cerebral vessels were normal, and only minimal atherosclerosis was noted in the aorta and coronary vessels. A review of the literature emphasizes the rarity of clinically significant artery atherosclerosis in the younger age group.

BERNSTEIN

Caroll, K. K.: Rape Oil and Cholesterol Metabolism in Different Species with Reference to Experimental Atherosclerosis. Proc. Soc. Exper. Biol. & Med. **94:** 202 (Jan.), 1957.

Numerous studies of experimental atherosclerosis have provided ample evidence of differences in metabolism of cholesterol in different species of animals. While the rat is very resistant to its production by cholesterol feeding: a marked increase in adrenal cholesterol resulted from feeding with rape oil. This contrasts with results obtained with rabbits, guinea pigs, chickens and dogs in which dietary cholesterol tends to be deposited more readily but in which rape oil is ineffective in causing a rise in adrenal cholesterol. The differences in response do not appear to be due to species differences in digestibility of rape oil but are probably related to differences in metabolism of phospholipids.

AVIADO

Dury, A.: Lipid Distribution and Metabolism in Two Areas of Aorta of Normal and Cholesterol-fed Rabbits. Proc. Soc. Exper. Biol. & Med. **94:** 70 (Jan.), 1957.

When cholesterol-fed rabbits are killed at successive periods gross, discrete atherosclerotic lesions appear first in the aortic arch and only much later in the rest of the aorta. The descending aortic limb has significantly lower total lipid, primarily due to decreased neutral fat concentration, compared with the arch. The specific activity of phospholipid in the descending aorta is significantly greater than that of the aortic arch of normal rabbits but this distinction is not found in the rabbits on a high-cholesterol diet. This is due to an increased rate of formation of phospholipid on the aortic arch (in fed rabbits) and probably is related to the development of atheromatous lesions. Although these facts suggest some fundamental metabolic differences between certain areas of the aorta, their possible relationship to the pathogenesis of atherosclerosis must await further studies of arterial tissue metabolism.

AVIADO

BLOOD COAGULATION AND THROMBOEMBOLISM

Gordin, R., and Laurent, L. E.: Mesenteric Thrombosis and Embolism. Report of 47 Cases. Acta med. scandinav. **154:** 267 (May 26), 1956.

A series of 47 patients with mesenteric thrombosis were observed during a period of 17 years. In 42 patients the diagnosis was confirmed at operation or autopsy. Occlusion of the superior mesenteric vessels was present in all instances. Arterial thrombosis or embolism was present in 37 patients and venous thrombosis was found in 5. There were 5 unverified cases, 3 of whom were given anticoagulants and all of whom survived. Cardiac disease was the causative factor in 28 patients, 21 of whom had atrial fibrillation. Malignant tumors were present in 4 patients and inflammation was present in 7. In some patients the infarction developed insidiously without any alarming symptoms for several days and in 5 patients there were no abdominal symptoms. Fourteen patients were operated upon and 3 survived. The authors believe that if the extent of the lesion permits, the treatment of choice in this disorder is resection of the involved portion of the bowel. Adequate fluid therapy in the postoperative period is very important. Anticoagulant therapy after operation is also important in order to prevent the development of new emboli or an extension of the thrombosis and intestinal gangrene. If resection is not possible, the condition apparently responds in some instances to anticoagulant therapy alone. The authors believe that if hemostasis is carefully performed at the time of surgery, anticoagulant treatment, preferably with heparin, can be begun on the day after operation.

ROSENBAUM

Sinapius, D.: Venous Thrombosis in the Cubital Region. Arch. Kreislaufforsch. **24:** 26 (June), 1956.

Of 63 routine autopsies on persons subjected to venipuncture, thrombosis of the cubital veins was found in 80 per cent. The thrombosis was attributed to mechanical lesion of the venous wall, combined with changes in blood composition due to injection and probably also circulatory stasis preceding death. Morphologic lesions of the endothelium caused by injected substances could not be found. In 14 patients organization of thrombi was present. Embolism of cubital venous thrombi could not be proved with certainty, but small pulmonary embolisms appeared likely.

LEPESCHKIN

Tuller, M. A.: Amniotic Fluid Embolism, Afibrinogenemia, and Disseminated Fibrin Thrombosis.

Case Report and Review of the Literature. Am. J. Obst. & Gynec. **73:** 273 (Feb.), 1957.

The syndrome of sudden dyspnea, cyanosis, and extreme shock occurring intrapartum or immediately post partum in association with a strenuous labor and clinical and pathologic findings of cor pulmonale is described as attributable to amniotic fluid embolism. Afibrinogenemia has been demonstrated in 1 patient and presumed to be present due to incoagulability of the blood in 4 others in the medical literature. The present case was a 38-year-old gravida 3, para 2 who developed afibrinogenemia during Pitocin induction complicated by shock, oliguria and death on the eighth post partum day. At autopsy, multiple fibrin emboli in the small vessels of most organs were found. Extensive necrosis of the pituitary gland was present. Afibrinogenemia was described as resulting from intravascular coagulation attendant upon release of thromboplastic material into the circulation.

SHUMAN

Kennan, A. L., and Bell, W. N.: Blood Coagulation during Normal Pregnancy, Labor, and the Puerperium. Am. J. Obst. & Gynec. **73:** 57 (Jan.), 1957.

The mechanism of blood coagulation was examined serially in 20 normal pregnant patients from the thirty-fourth week through delivery and the early part of the puerperium. The levels of fibrin and platelets were found to decrease near term. Clot retraction time and prothrombin time were reduced in early labor. A sharp stimulus for platelet production was noted during labor. The utilization of fibrinogen for hemostasis during delivery is parallel to that noted during surgical procedures. During the puerperium, there was an increase in platelets, prothrombin, and fibrinogen. These changes may contribute to the embolic phenomena that are common at this time. The normal fluctuations during parturition of the factors involved in blood coagulation would not have caused any major bleeding difficulties.

SHUMAN

Phillips, L. L., Montgomery, G., Jr., and Taylor, H. C., Jr.: The Role of the Fibrinolytic Enzyme System in Obstetrical Afibrinogenemia. Am. J. Obst. & Gynec. **73:** 43 (Jan.), 1957.

The plasma of 10 women with hemorrhage due to afibrinogenemia were examined for fibrinogen content, fibrinogenolytic and fibrinolytic activity, the inhibitors of such activity, and the hydrolytic products of enzyme action. Significant levels of fibrino- and fibrinogenolytic activities were found in most of the patients. Fibrinogen levels were reduced to less than 25 mg. per cent in 6 patients, 3 were found between 55 and 89 mg. per cent, 1 had a minimum level of 170 mg. per cent. After fibrinogen therapy bleeding usually showed a marked decrease within 30 to 60 minutes and changed to a normal lochia within 3 hours, at which time fibrinogen levels had risen to 120 mg. per cent or higher. The lysis of serially diluted plasma clots disclosed considerable fibrinolytic activity in all cases. This change disappeared rapidly after intravenous fibrinogen infusion. Inhibitor levels showed a concomitant return to normal. It is suggested that proteolytic activity may be at least partially responsible for the fibrinogenopenia observed in these patients.

SHUMAN

Drinan, F. W., Adamis, D., Sise, H. S., and Moloney, W. C.: Studies on the Anticoagulant Phenindione. III. Its Use in Ambulatory Patients. Am. Heart J. **53:** 284 (Feb.), 1957.

In 33 patients the anticoagulant phenindione was employed on a long-term basis to maintain the prothrombin time at therapeutic protective levels (between 26 and 36 seconds originally, but between 20 to 30 seconds in the latter part of the study). The dose of phenindione required usually decreased during the first 3 months, but thereafter remained constant in 50 per cent of the cases and required little changes in the others. Because of its steadier effect on the prothrombin time with resultant less dosage adjustment and less close supervision being necessary, phenindione is considered by the authors to be superior to Dicumarol in long-term anticoagulation. In this series nearly all patients noted minor evidences of a bleeding tendency, and significant bleeding occurred in 27 per cent of the cases. During 565 patient months of treatment thromboembolic episodes occurred twice in 2 patients. Other than bleeding no toxicity was observed.

SAGALL

Sise, H. S., Moloney, W. C., and Guttas, C. G.: Studies on the Anticoagulant Phenindione. II. Details Regarding Its Administration in Two Hundred Cases. Am. Heart J. **53:** 132 (Jan.), 1957.

The present report is based on the routine use of phenindione in 200 consecutive hospitalized patients in whom anticoagulant therapy was indicated. In the average patient the initial dose was 200 mg., followed by 100 mg. in 12 hours. For predictable effects the maintenance dose had to be given every 12 hours. The dosage varied and ranged from 29 to 400 mg. to keep the prothrombin activity between 5 and 10 per cent of normal. Changes in dosage requirement were seen, as was a cumulative effect with the same dose in some instances. The dissipation of effect usually occurred within 72 hours and, oftentimes, within 36 hours. Stabilization of dose did not occur for 6 days or more. In 21 patients (10.5 per cent) bleeding occurred, but this was slow and readily responded to vitamin K emulsion. The present study indicated some superiority of phenindione over bishydroxycoumarin in clinical use

only as a result of the more rapid onset and dissipation of its effect.

SAGALL

Jordan, F. L. J., and Nandorff, A.: The Familial Tendency in Thrombo-embolic Disease. Acta med. Scandinav. **156:** 267 (Dec. 31), 1956.

The authors report 22 instances recorded in the literature and 21 patients from their own clinic in whom there was evidence suggesting a familial occurrence of thrombosis, thrombophlebitis, or thromboembolic disease. These observations are believed to be of some importance in the problem of the etiology of thromboembolic disease and to argue for a more liberal prophylactic use of anticoagulants in patients with a familial history of thrombosis.

ROSENBAUM

de Groot, V. M., and Friedenwald, J. S.: Thrombi in the Ciliary Veins of Eyes from Newborn Infants. Am. J. Ophth. **43:** 93 (Jan.), 1957.

Fresh thrombi were found in various parts of the ciliary veins of 10 stillborn or newborn infants autopsied since 1950. Three of them had thrombi in other organs. Review of various data regarding the infants and their mothers gave no adequate explanation for occurrence of the ciliary vein thrombosis, a previously unobserved phenomenon.

ROGERS

Mayer, G. A., and Connell, W. F.: The Anticoagulant Effect of a New Coumarin Derivative—Sintrom (Geigy)—and Its Control by Standardized Clotting Time. Canad. M. A. J. **76:** 272 (Feb. 15), 1957.

The daily oral administration of Sintrom to 42 patients, most of whom had acute myocardial infarction or acute coronary insufficiency, was guided by daily standardized clotting times (SCT), the normal value being 9.69 to 0.55 minutes. Therapeutic prolongation of the SCT to 15 to 20 minutes was reached after an average induction period of 4.3 days and was obtained on 71 per cent of the total of 866 treatment days. Neither hemorrhagic accident nor thromboembolism was noted while the SCT was in the therapeutic range, and it was concluded that Sintrom is a satisfactory anticoagulant for short-term therapy.

ROGERS

DeLand, F. H., and Bennett, W. A.: Death Due to Bone-Marrow and Tumor Embolization in the Absence of Fracture. Report of a Case. Arch. Path. **63:** 13 (Jan.), 1957.

An example of massive pulmonary embolization followed by instantaneous death in a 71 year-old white man following transurethral prostatic resection is presented. The embolization was composed of bone marrow and metastatic tumor to the bone marrow. It was assumed that bone "concussion" of the vertebrae, caused by the strain of cystoscopy or moving from the bed, or both, resulted in medullary fracture of bone marrow previously weakened by carcinomatous metastasis. No comparable case has been noted in the literature.

MAXWELL

CONGENITAL ANOMALIES

Brandenburg, R. O., DuShane, J. W.: Clinical Features of Persistent Common Atrioventricular Canal. Proc. Staff Meet. Mayo Clin. **31:** 509 (Sept. 19), 1956.

It is possible to define 3 clinical types of persistent common atrioventricular canal. The first is atrial septal defect (ostium primum type) without valvular insufficiency. Hemodynamically this lesion is identical with atrial septal defect. Significant pulmonary hypertension may be associated with this lesion but seems to be relatively infrequent. The second is atrial septal defect (ostium primum type) with valvular insufficiency (both atrioventricular valves or only the mitral valve). Pulmonary hypertension is more frequently present than in the first type The third is atrial and ventricular defect with atrioventricular valvular insufficiency. Pulmonary hypertension is frequently present. Roentgen examination has not been particularly helpful in differentiation in most patients. In adult patients the cardiac silhouette has not been larger than in patients with usual atrial septal defects. The cardiac silhouette may be only slightly or markedly enlarged. The pulmonary artery shadow and pulmonary vascular markings are increased. Cardiac enlargement involves predominantly the right side of the heart, a fact that makes mild degrees of left ventricular and left atrial enlargement difficult to detect. The electrocardiogram is an important tool of the clinician. This aspect of the clinical appraisal of the patient with this defect has proved a most important diagnostic aid. From a careful evaluation of the authors experiences with this lesion in the past year they believe that in the future they shall be able to suspect this defect in most instances on the basis of clinical data. With the additional aid of hemodynamic data from the catheterization laboratory a decision regarding surgical treatment in an individual case can usually be made on a sound basis.

SIMON

Anderson, J. P.: Coexistent Aplastic Anemia and Coarctation of the Aorta. Arch. Dis. Childhood **31:** 131 (Apr.), 1956.

A case of a 14 year old boy who had aplastic anemia and a coarctation of the aorta is reported. The child died of a massive cerebral hemorrhage secondary to thrombocytopenia. Speculation is presented on a possible relationship between the congenital cardiovascular abnormality and the bone

marrow deficit. It is suggested that both may represent a "forme fruste" of the Fanconi syndrome.

HARVEY

Quintin, P., and Duluc, J.: Functional Clinical Tests in a case of Ebstein's Disease. Arch. mal. coeur **49:** 346 (Apr.), 1956.

A 21-year-old soldier who died suddenly showed at autopsy complete fusion of the posterior and incomplete fusion of the septal leaflet of the tricuspid valve with the endocardium. The man had no complaints, and all function tests except those of Lian and Demeny were normal. A nonpropagated mesocardiac systolic murmur could be heard, and the electrocardiogram showed only left axis deviation.

LEPESCHKIN

Bret, J.: Extreme Trilogy of Fallot. Arch. mal. coeur **49:** 337 (Apr.), 1956.

Nearly complete atresia of the pulmonary artery with intact ventricular septum and persistence of the foramen ovale and the ductus arteriosus was seen in 2 girls, comprising about 1 per cent of all congenital heart disease and 6 per cent of all trilogies of Fallot. In the first case the pulmonary orifice barely admitted a pin at autopsy; in the second case this orifice admitted a 1-mm. bougie during a valvulotomy operation, after which the extreme cyanosis disappeared almost completely, but the size of the heart increased. The electrocardiogram in both cases showed marked right axis deviation, tall monophasic R with inverted T in V_1 and deep S in V_2–V_6.

LEPESCHKIN

Burchell, H. B.: Total Anomalous Pulmonary Venous Drainage: Clinical and Physiologic Patterns. Proc. Staff Meet., Mayo Clinic **31:** 161 (Mar.), 1956.

When the pulmonary veins are transposed, to drain anomalously only into the right side of the heart, it is evident that the left heart would be bloodless unless there were a communication between it and the right side. In its simplest form, this communication is a patent foramen ovale. As would become evident in a study of any diagram of the fetal circulation, the anomalous circulation associated with total pulmonary venous drainage causes no disturbance in the fetus, but in postnatal life a gross inefficiency in the mammalian-type circulation exists.

In any differentiation of types of total anomalous pulmonary connection, the presence or absence of pulmonary hypertension is of paramount importance. Those with pulmonary hypertension could be subclassified into those in which the pulmonary hypertension is related to obstruction of the outflow of blood from the lungs, where a high "wedge pressure" in a pulmonary artery could be recorded, and those in which pulmonary arteriolar obstruction occurs pari passu with increased pulmonary blood flow. The clinical picture in infants is different from that in older children or adults and most often is manifested by pulmonary and systemic venous congestion (heart failure) appearing in the early neonatal months. While the infants may be intermittently cyanotic, cyanosis is not a characteristic of the condition at birth and even not during the course of the failure except at its termination.

While the size of the foramen ovale or interatrial orifices which allow blood to reach the left side may be critical, it would appear that this is not always the main factor in causing the heart failure, but rather, the right heart may fail in relationship to its efforts to maintain a high flow of blood against an increasing pulmonary resistance. One clinical syndrome that has been suggested that might tip one off to the presence of this total anomalous drainage into an abdominal vein would be the evidence of pulmonary congestion when a child strains.

In concluding these remarks, a definite conflict of opinion may be registered with those who would recommend that surgical therapy of total anomalous drainage be restricted to those patients with progressive disability. When symptoms are progressively severe and the patient is disabled, not only would operative risk be high, but the chances of restitution of normal circulatory function would be meager because of nonregressive pulmonary vascular changes. When the diagnosis can be made, the recommendation for surgical intervention exists if severe pulmonary hypertension is absent, and the surgeon then picks the time when technically it can be most competently and safely performed.

SIMON

Calazel, P., Bollinelli, R., Cassagneau, J., Esclavissat, M., Serena, G., and Meriel, P.: Abnormally Well Developed Pulmonary Vascularization in Certain Tetralogies of Fallot. Arch. mal. coeur **49:** 206 (Mar.), 1956.

In 4 patients in whom a tetralogy could be proved by cardiac catheterization (entrance of the catheter into the aorta, large pressure gradient at the pulmonary artery) the pulmonary vessels were dense and pulsated in 2 patients. In 2 instances a partial explanation of these unusual findings could be given by assuming a persistent ductus arteriosus. Another explanation is the development of a pulmonary collateral circulation intense enough to show vascular pulsation. A third possibility is pulmonary regurgitation. Finally, it is possible that in some cases of tetralogy the intraventricular communication is more important than the pulmonary stenosis.

LEPESCHKIN

Scebat, L., Durand, J., and Renais, J.: Pathogenetic and Therapeutic Study of Certain Cyanotic Crises Occurring in Congenital Heart Disease. Arch. mal. coeur **49:** 246 (Mar.), 1956.

In 4 patients (interventricular communication, intraatrial communication, aorticopulmonary fistula, and pentalogy of Fallot) cardiac catheterization disclosed that the pulmonary pressure showed no appreciable change, while the systemic pressure was always lowered whenever cyanosis was present. Oxygen inhalation did not improve the arterial oxygen saturation, but infusion of norepinephrine raised the systemic pressure and improved this saturation immediately.

LEPESCHKIN

Mouquin, M., Durand, M., Metianu, C., and Beyda, D. Single Ventricle. An Anatomical and Clinical Observation in a Person Twenty Years Old. Arch. mal. coeur **49:** 259 (Mar.), 1956.

This male patient with early cyanosis showed an only slightly enlarged heart, a vertical QRS axis with late wide R′ in leads V_1–V_2, a transition zone at V_5, absent Q waves, pointed T waves in V_3–V_6 and elevation of P in leads II and III. Autopsy showed a single ventricle with a common quadricuspid A-V valve and large atrial septum defect; the wide aorta originated anteriorly while the very narrow pulmonary artery originated from the same ventricle posterior to it. The relatively long life of the patient is attributed to extensive pulmonary anastomoses. The most striking observation is that normal right and left ventricular patterns were seen in precordial leads in the presence of a single ventricle of nearly uniform thickness.

LEPESCHKIN

Boesen, I., Lind, J., Merrild-Hansen, B., Rosendal, T., Storm, O., and Wegelius, C.: The Diagnosis of Congenital Heart Disease in Infants by Catheterization and Selective Angiocardiography. Brit. Heart J. **18:** 355 (May), 1956.

The authors report their findings in 50 infants with congenital heart disease studied by simultaneous heart catheterization and angiocardiography. All examinations are done under anesthesia. Contrast substance, 1.1 to 1.9 ml. per Kg. body weight, is injected within 1 second through a catheter passed through the saphenous vein.

The authors recognize that these studies are not performed under physiologic conditions. The pressure readings are unstable. A difference of at least 1 volume per cent in oxygen saturation must be present to be diagnostic of a shunt between the pulmonary artery and right ventricle or right ventricle and right atrium. Between the right atrium and venae cavae, the difference must be at least 2 volumes per cent. The left atrium was catheterized in 15, only 11 of whom had signs of an intraatrial shunt. In 5, the aorta was catheterized through the ductus arteriosus.

Direct intracardiac injection of contrast substance permits excellent visualization of that part of the heart which is of special interest.

This combined technic, together with the clinical findings, permits a satisfactory degree of certainty of the pathologic, anatomic, and physiologic cardiac abnormalities.

SOLOFF

Dammann, J. F., Jr., and Ferencz, C.: The Significance of the Pulmonary Vascular Bed in Congenital Heart Disease. I. Normal Lungs. II. Malformations of the Heart in which there is Pulmonary Stenosis. Am. Heart J. **52:** 7 (July), 1956.

Lung sections from autopsy and biopsy material from a large number of patients with congenital heart disease were studied in comparison with sections from 100 normal patients. The pulmonary vascular changes in small muscular pulmonary arteries associated with, or lying clearly apart from, small bronchioles was evaluated. The total transverse diameter of such a vessel was measured. The thickness of each layer, adventitia, media, and intima, was recorded. The diameter of the lumen was divided by twice the thickness of the media and intima added together, thus giving a ratio of lumen size to wall thickness. The lumen:wall ratio was placed against the age of the patient. Microscopic examination of the lungs of 50 patients over 2 months of age in whom a clear-cut anatomic pulmonic stenosis was present revealed an essentially normal pattern of evolution of the pulmonary vascular bed. The small pulmonary arteries were thin-walled with wide lumens and were similar to those in normal lungs.

RINZLER

Coursley, G., Ivins, J. C., and Barker, N. W.: Congenital Arteriovenous Fistulas in the Extremities. An Analysis of Sixty-nine Cases. Angiology **7:** 201 (June), 1956.

Detailed clinical findings are presented in 69 patients with congenital arterial venous fistulas seen at the Mayo Clinic from 1935 to 1953. The authors point out that arteriography merely provided corroborative information and that correct interpretation of arteriograms required extensive experience. No cardiac symptoms were thought to be referable to the fistulas. Treatment of these lesions has been difficult and must be individualized. Some patients were successfully managed with control of edema and healing of ulcerations through the use of elastic stockings and heel lifts. In others, ligation and stripping of varices and a direct attack on the fistula were performed. An appreciable number of patients required major amputation.

WESSLER

Dexter, L.: Atrial Septal Defect. Brit. Heart J. **18:** 209 (Apr.), 1956.

The results of cardiac catheterization in 60 in-

dividuals with atrial septal defect were analyzed in an attempt to understand the nature of this disorder and some of its complications.

When the defect is small, left atrial pressure is greater than right atrial. When the defect is large, the pressures in each atrium during diastole are equal. Flow continues from right to left and mostly during diastole because of greater distensibility of the right atrium. In diastole, there is a free communication between respective ventricles. A small right to left atrial flow may also be present.

The left ventricular output is not above normal. The right ventricular and pulmonary arterial pressures are normal unless flow is greater than 10 liters per minute per $M.^2$, which raises pressures slightly, or unless there is pulmonary vascular disease, which may raise pressures considerably.

The incidence of cyanosis increases with age. The severe grades of cyanosis are associated with the smallest right ventricular outputs.

Minor degrees of cyanosis are explainable on mixing of systemic and pulmonary venous blood streams in the common atrium. This mixture is enhanced when the right ventricular pressure approaches the systemic. A high right ventricular pressure is associated with the smallest right ventricular outputs and with high pulmonary vascular resistance.

The cause for increase in pulmonary vascular resistance is not clear but it may be due to pulmonary thrombosis or embolism either of which is a common event late in the natural history of atrial septal defect.

Left ventricular output remains fairly constant even with rising end diastolic pressures. On the other hand, the right ventricular output may be large or small, regardless of the height of its end-diastolic pressure. Digitalis can increase right ventricular flow without changing its end-diastolic pressure. It is therefore concluded that right ventricular failure is manifested by a decrease in right ventricular flow without change in its end-diastolic pressure. On the other hand, left ventricular failure is characterized by increase in its end-diastolic pressure, which is transmitted to both atria and to the right ventricle.

The right ventricle fails because (1) of the increasing work it performs (pressure and flow), (2) of the appearance of pulmonary vascular disease, and (3) of the production of functional tricuspid incompetence.

The left ventricle fails because of the presence of relatively minor lesions imposing a burden on the left ventricle such as mitral valvulitis, hypertension, and endocardial fibroelastosis of the left ventricle.

Finally, Lutembacher's syndrome is rare and can be diagnosed only by demonstrating a pressure gradient between the left atrium and the left ventricle.

SOLOFF

Wakai, C. S., and Edwards, J. E.: Developmental and Pathologic Considerations in Persistent Common Atrioventricular Canal. Proc. Staff Meet., Mayo Clin. **31:** 487 (Sept.), 1956.

The complete and partial varieties of persistent common atrioventricular canal appear to represent different degrees of malformation in relation to the atrioventricular endocardial cushions. In each instance, there is an interatrial communication. In the complete variety interventricular communication is frequent, while in the partial variety this is uncommon. Incompetence of the mitral valve may be an integral, though not necessary, feature of the malformation in the partial variety. In the complete form, insufficiency of both atrioventricular valves may exist. Death at an early age is usual in the complete variety, while longer survival is more frequent in the partial variety.

SIMON

Wakai, C. S., Swan, H. J. C., and Wood, E. H.: Hemodynamic Data and Findings of Diagnostic Value in Nine Proved Cases of Persistent Common Atrioventricular Canal. Proc. Staff Meet., Mayo Clin. **31:** 500 (Sept.), 1956.

The hemodynamic data and findings of diagnostic value obtained during cardiac catheterization are presented in 9 proved cases of persistent common atrioventricular canal. Four of the 5 adults were found to have normal pulmonary artery pressures and pulmonary vascular resistances. Pulmonary hypertension was present in 1 of the 5 adults and in all 4 children studied. The systemic blood flows were found to be normal in all cases. The increased pulmonary blood flows were due to large left-to-right shunts occurring at both the atrial and the ventricular levels, but in most cases chiefly at the atrial level.

The catheterization features that assist in the differentiation of persistent common atrioventricular canal from atrial septal defect of the usual variety are: (1) the low position of the shaft of the catheter in the cardiac silhouette when the catheter tip has been manipulated into the left ventricle; (2) evidence of additional arterialization in the right ventricle over that in the right atrium, and (3) the absence or decreased degree of preferential left-to-right shunting of blood from the right lung.

SIMON

Swan, H. J. C., Toscano-Barboza, E., and Wood, E. H.: Hemodynamic Findings in Total Anomalous Pulmonary Venous Drainage. Proc. Staff Meet. Mayo Clin. **31:** 177 (March), 1956.

The diagnosis of total anomalous pulmonary venous drainage rests upon the demonstration that the saturation of pulmonary artery blood equals or exceeds that of systemic artery blood, and that by dye-dilution curves the right ventricle represents a site that is functionally upstream to the right

atrium in the pathway to the systemic circulation. The anatomic basis for these findings may be either a common atrium or an anomalous connection of all the pulmonary veins to the right atrium or one of its tributaries. In the latter instance, the presence of abnormal elevation of the oxygen saturation of blood samples drawn from the inferior or superior vena cava, innominate vein, or coronary sinus, or the course of a cardiac catheter when entering a pulmonary vein may assist in arriving at a correct anatomic diagnosis.

SIMON

Stewart, A. M., and Wynn-Williams, A.: Combined Tricuspid and Pulmonary Atresia with Juxtaposition of the Auricles. Brit. J. Radiol. **29:** 326 (June), 1956.

The authors present a case report of a 13 month old cyanotic child with periodic respiratory distress, cardiac enlargement to the left, good first and second heart sounds in all areas, and a soft systolic murmur. Roentgenograms indicated an enlarged left ventricle, no evidence of left or right atrial enlargement, and a distinctly small right ventricle, as judged by failure of the cardiac shadow to project toward the anterior chest wall in the left anterior oblique position. The electrocardiogram showed the pattern of left ventricular hypertrophy.

At autopsy the following were noted: tricuspid atresia with a rudimentary right ventricle; atretic pulmonary artery trunk with almost normal-sized primary branches fed via a patent ductus arteriosus; large atrial septal defect; and a small ventricular septal defect with an overriding but otherwise normal aorta. The atrial tips were juxtaposed to the left of the aorta. Death apparently was precipitated by thrombosis of the left pulmonary artery.

SCHWEDEL

Sandifer, S. H.: Mild Coarctation of the Aorta with Normal Blood Pressure. Am. Heart J. **51:** 761 (May), 1956.

Six young adult men 19 to 29 years of age were studied mainly because of the presence of a systolic murmur. Poststenotic dilatation, as demonstrated by chest roentgenograms in the left anterior oblique view with barium swallow, was present in all cases, and in 2 instances the area of coarctation could be seen on the plain posteroanterior chest roentgenogram. The heart size was normal by x-ray in 3 cases and slightly enlarged in the other 3. The electrocardiogram was normal in 5 patients and showed left ventricular hypertrophy in 1. In all but 1 case (systolic pressure was 155 mm. Hg) the brachial artery pressure by direct measurement was normal. By palpation, the femoral artery pulsations were considered to be normal in 1 patient, slightly decreased in another, decreased in 3, and feeble in the remaining patient. The author concludes that when a murmur is heard at the level of the second to the fourth intercostal space beneath the sternum, and especially when this murmur is well heard in the back, coarctation of the aorta should be suspected, despite the level of the brachial blood pressure by sphygmomanometry. This becomes especially pertinent if the femoral pulses, by palpation or measurement, are considered to be present but diminished.

RINZLER

Zion, M. M.: Mitral Stenosis Associated with Anomalous Pulmonary Venous Drainage into a Left Superior Vena Cava. Brit. M. J. **1:** 1020 (May 5), 1956.

The author describes a 42-year-old woman with what was fairly typical clinical mitral stenosis with additional signs of tricuspid regurgitation. At operation the surgeon discovered a large left superior vena cava draining the left superior pulmonary vein, joining the left innominate vein and presumably carrying blood that found its way eventually to the right atrium via the normal right superior vena cava. The pulmonary artery was enormous. Tight mitral stenosis in a mobile, noncalcified valve was found but no regurgitation. Satisfactory commissurotomy was possible. After operation improvement was in general satisfactory. The apical diastolic rumble disappeared but signs of triscuspid regurgitation, a pansystolic murmur at the lower end of the sternum, and an opening snap (? mitral) persisted. Cardiac catheterization data obtained after operation are presented.

It is of interest that the preoperative radiograph presented by the author shows much greater radiolucency of the left upper lung field, which was not subjected to the congestive effects of pulmonary venous hypertension.

MCKUSICK

Peel, A. A. F., Semple, T., Kelly, J. C., and Blum, K.: Anomalous Venous Drainage with Death from Cardiac Catheterisation. Scot. M. J. **2:** 83 (Feb.), 1956.

The rarely reported cases of death during or following cardiac catheterization are reviewed. The authors describe a 10-year-old girl who at autopsy was found to have the right subclavian and jugular veins entering the right atrium and left subclavian and jugular veins entering the left atrium. No innominate vein connected the left and right superior venae cavae. There was a patent ductus arteriosus. The left atrium, left ventricle, and aorta were small, but the aorta became larger beyond the patent ductus.

Clinically the patient had universal cyanosis, clubbing of the toes but not the fingers, a systolic murmur at the apex and left sternal border, hepatomegaly.

Cardiac catheterization was attempted from the left arm because the right arm had been used for

angiocardiography. Trial of 3 catheters was unsuccessful in passage beyond the level of the first rib. The patient was anesthetized with thiopentone supplemented with Flaxedil. Shortly after the unsuccessful attempts to pass the catheter, it was noted that the right side of the face and right arm, usually cyanotic, were now bright pink. The left side of the face and left arm were more cyanotic than ever. The right jugular vein was filled; the left could not even be identified. The right radial pulse was imperceptible. Respiratory and cardiac activity ceased during the next half hour.

The authors suggest that blockage of entry of blood to the left ventricle resulted from spasm at the junction of the left jugular and subclavian veins. What blood was put out was now fully oxygenated; hence the pink color of the right side of the face and weak right radial pulse. It is further suggested that a large flow through the patent ductus from pulmonary artery to aorta may account for the increased cyanosis in the left side of the body.

The complicated story suggests that catheterization via the left arm is hazardous in patients in whom anomalous venous drainage of this type is suspected clinically.

McKusick

Gasul, B. M., and Fell, E. H.: Salient Points in the Clinical Diagnosis of Congenital Heart Disease. Based on a Nine-Year Study of 1,395 Patients. J.A.M.A. **161:** 39 (May 5), 1956.

Congenital malformations of the heart have been studied in 1,395 patients. In the vast majority, a clinical diagnosis could be made without angiocardiography and without cardiac catheterization. All that was usually necessary in order to arrive at a clinical diagnosis was to correlate the history, physical, fluoroscopic, roentgenologic, and electrocardiographic findings. In this series of cases, however, in addition to the above-listed examinations, the diagnoses were confirmed by 850 angiocardiograms, 450 cardiac catheterizations, as well as 300 autopsies. The order of frequency of the 13 noncyanotic types reported in this series was ventricular septal defect, patent ductus arteriosus, atrial septal defect, coarctation of the aorta, isolated pulmonary stenosis, aortic and subaortic stenosis, primary endocardial fibroelastosis, idiopathic dilatation of the pulmonary artery, vascular rings, anomalous left coronary artery, aortic septal defect, ruptured sinus of Valsalva, and glycogen storage disease. The order of frequency of the 9 cyanotic types was as follows: tetralogy of Fallot, complete transposition of the great vessels, pulmonary stenosis with atrial and ventricular septal defect, Eisenmenger complex, tricuspid atresia, persistent truncus arteriosus, levocardia, Taussig-Bing heart, and anomalous drainage of all pulmonary veins.

Kitchell

Nash, F. W., and Mackinnon, D.: Cor Triatriatum: Congenital Stenosis of the Common Pulmonary Vein. Arch. Dis. Childhood **31:** 222 (June), 1956.

A case is reported of a 7-week-old male infant who died of heart failure from unknown cause. He was normal in all respects by physical examination except for slight cyanosis due to enlargement of the heart. Autopsy revealed an enlarged heart with right ventricular hypertrophy, and a 2-chambered left atrium separated by a thick membrane through which there was a very small opening 1 mm. in diameter. The pulmonary veins emptied into the posterosuperior chamber. The anteroinferior chamber communicated with the left ventricular chamber through a normal mitral valve. No other congenital abnormalities were present. The literature on this anomaly is reviewed. The clinical features are rapidly developing heart failure, absence of murmurs, tachycardia, right axis deviation, and right-sided hypertrophy. Opinion is expressed on the embryologic development of this anomaly. A plea is made for consideration of this anomaly in infants with heart failure presenting the above-listed clinical features. It might well lend itself to surgical amelioration. It is suggested that the surgical approach, when suspected, be made through the pulmonary artery to avoid entering the normal-appearing anteroinferior chamber, which would cause one to miss the lesion.

Harvey

Kilby, R. A., DuShane, J. W., Wood, E. H., and Burchell, H. B.: Ebstein's Malformation: A Clinical and Laboratory Study. Medicine **35:** 161 (Sept.), 1956.

The authors discuss the findings in 9 cases of Ebstein's malformation seen at the Mayo Clinic and review the data of 71 reported cases in the literature. Cyanosis was present in 84 per cent of the previously reported cases and was present at some time in each of the authors' cases. Most patients showed cyanosis at birth or in early infancy, but in over one third of the patients there was a substantial delay (up to 52 years) in its appearance. It was practically always associated with an atrial septal defect.

The basic deformity of the malformation consists of a downward displacement of the posterior leaflet of the tricuspid valve, with adhesion to the ventricular wall, while the anterior leaflet may form a long veil-like structure. The size and thickness of the right ventricle are variable. The tricuspid orifice may be small enough to amount to a true stenosis. The large triscuspid leaflet may be pushed toward the free wall of the ventricle, occluding its cavity and preventing filling. During systole, blood behind the leaflet may be regurgitated into the atrium proper.

Auscultatory findings are variable. Double murmurs can be detected in almost half the patients,

systolic murmurs alone in a few, and diastolic murmurs alone in even fewer. A loud third heart sound is present in about one third of the cases. Phonocardiograms in 7 patients exhibited systolic and diastolic murmurs in all, murmurs of atrial contraction in 4, and loud third heart sounds in 3 instances.

Electrocardiographic findings are generally characteristic. Right bundle-branch block, usually atypical, is the chief finding. The tracings are apt to show RR′ deflections in right chest leads but frequently with low voltage of R and excessive splintering of R′. Increased sharpness and amplitude of P waves, and A-V conduction defects are also common. Supraventricular arrhythmias are fairly frequent.

The roentgenographic appearance is rather uniform. The heart is moderately to greatly enlarged, with a globular shape and a relatively narrow vascular pedicle in the posteroanterior view. Angiocardiograms have been used to demonstrate the location of the R-L shunt so commonly present. In addition to showing the atrial septal defect a huge thin-walled right atrium can be shown. Because of stasis in this chamber the pulmonary circulation is poorly outlined.

Cardiac catheterization data of 27 cases were reviewed by the authors. Typically, the catheter enters a huge "atrial" chamber that occupies the space normally taken by the right ventricle. Mean atrial pressures are normal or increased. Right ventricular and pulmonary artery pressure curves are usually normal. Evidence of a R-L shunt at an atrial level is found in almost all patients with arterial oxygen unsaturation. Only 1 instance of a ventricular septal defect has been reported.

Among 32 autopsied cases, heart failure was present in one third. Seven patients died suddenly with no obvious cause. Pulmonary tuberculosis, cerebral abscesses, and other infections occurred in one third of the cases. Paradoxic embolism was proved in 2 other cases. Of 4 cases operated upon at the Mayo Clinic 1 survived and is greatly improved.

ENSELBERG

Soloff, L. A., and Zatuchni, J.: Embolic Occlusion of Patent Foramen Ovale. Arch. Int. Med. **98:** 344 (Sept.), 1956.

The characteristic picture of embolic occlusion of a patent foramen ovale is illustrated by a case report. This syndrome should be suspected in a person without apparent heart disease who develops peripheral thrombophlebitis followed by pulmonary and later systemic embolism with persistent cyanosis and subsequently dies abruptly with intensification of the cyanosis and bulging neck veins. The electrocardiogram may show signs suggestive of pulmonary embolism.

When sudden closure of the foramen ovale occurs in a person with pre-existing pulmonary hypertension a further rise of pressure within the right heart ensues, producing abruptly bulging neck veins and marked cyanosis. Additional pulmonary emboli may further intensify the picture.

BERNSTEIN

Marquis, R. M.: Longevity and the Early History of the Tetralogy of Fallot. Brit. M. J. **1:** 819 (Apr. 14), 1956.

Necropsy cases in patients 65 and 48 years of age are described. Previously, 10 patients surviving to 40 years of age or more have been described.

The author points out with quotation and portrait, that Nicolas Steno (Niels Stensen) of Stensen's duct fame, described Fallot's tetralogy in 1673. Pre-Fallot contributions by British cardiologists, especially James Hope (1839) and Thomas Peacock (1866), are reviewed.

MCKUSICK

Dent, E. D., Jr., and Fisher, R. S.: Single Coronary Artery: Report of Two Cases. Ann. Int. Med. **44:** 1024 (May), 1956.

Two patients with single coronary arteries were discovered accidentally during autopsy examinations. Both were white men, one 64 years of age and the other 56. Neither showed clinical evidence of absence of a coronary artery. In 1 patient the cause of death was arteriosclerotic heart disease with coronary occlusion and myocardial infarction. In the second patient no cardiovascular disease was clinically demonstrable. A single coronary artery, if not accompanied by evidences of cardiovascular disease or other anomalies of the heart, does not result in cardiac dysfunction. In individuals who have attained adulthood the condition of a single coronary artery is generally unassociated with any other cardiac abnormality. In children who die with a single coronary artery, it would appear that the premature death is attributable to the presence of other cardiac abnormalities. Longevity is apparently not altered by the presence of a single coronary artery. There is 1 case reported in the literature of an individual who died at the age of 80 years. The average age in adults is 45 years. Among 27 cases reported in adults, only 9 manifested evidences of heart disease as a cause of death. Even in these cases death was not connected with the presence of a single coronary artery. The total number of reported cases of single coronary arteries in adults and children is currently 43.

WENDKOS

Cooley, J. C., and Kirklin, J. W.: The Surgical Treatment of Persistent Common Atrioventricular Canal: Report of 12 Cases. Proc. Staff Meet. Mayo Clin. **31:** 523 (Sept. 19), 1956.

In 12 patients with common atrioventricular canal, operation has been performed at the Clinic. In the first 3, the atrial-well technic was used. In

the last 9, operation has been performed, since extracorporeal circulation through a mechanical pump-oxygenator had been developed and this technic was employed for them. In all cases, a prosthesis of ivalon sponge was utilized to close the defect. Six patients were male and 6 female. The ages varied from 10 months to 27 years, 5 patients being more than 20 years of age. All patients were symptomatic, the severity of symptoms varying from a 10-month-old child desperately ill to a 20-year-old man experiencing only mild exertional dyspnea and occasional bouts of paroxysmal tachycardia. All patients underwent cardiac catheterization preoperatively. In 7 of the 12 patients mitral insufficiency was demonstrated at operation. Nine patients have survived operation. Seven of these have not as yet undergone cardiac catheterization postoperatively, although in 5 a normal dye curve was obtained at the end of the operative procedure. By clinical evaluation all these appear to have an excellent result. Another patient had a complete closure of the defect proved by cardiac catheterization 6 months following operation. In one patient in whom the atrial-well technic was used, cardiac catheterization 7 months postoperatively revealed a residual left-to-right shunt of 35 per cent at the ventricular level. Preoperatively, the over-all shunt had been 76 per cent. The patient seemed clinically improved. There were 3 deaths in this group of 12 patients, 2 in 10-month-old children and 1 in a 5-year-old boy. One of these children died 12 hours postoperatively. Severe mitral insufficiency was identified at operation, before repair. The atrioventricular canal was repaired but nothing was done to the cleft in the mitral valve. The evidence is good that the death resulted from this unrelieved mitral insufficiency. Common atrioventricular canal presents a grave problem to the person afflicted. Fortunately, progress has been made both in diagnosis and in surgical treatment. Although problems in surgical therapy remain, there is reason for encouragement in the fact that repair has been accomplished in 12 patients, with 9 surviving and benefited by operation.

SIMON

Alcott, D. L., Sanfilippo, P., and Edwards, J. E.: Taussig-Bing Complex Associated with Anomalous Right Subclavian Artery Arising Proximal to Coarctation of the Aorta. Pediatrics **18:** 561 (Oct.), 1956.

A case report is presented of a female infant, who lived for 2½ months with persistent cyanosis, choking spells, and an increase in the size of the heart. At autopsy, a variant of the Taussig-Bing malformation was found. The aorta rose from the right ventricle, and the pulmonary artery arose from the right and left ventricle above a ventricular septal defect; about three quarters of the vessel arose from the left ventricle. The first branch of aortic arch was a common vessel that divided into right and left common carotid arteries. The second branch of the aortic arch was the left subclavian artery. Immediately beyond this was a coarctation, but arising from the posterior wall of the aorta just above the coarctation was an anomalous right subclavian artery. The right subclavian artery passed behind the esophagus to the right arm, and caused compression of the posterior aspect of the esophagus. In addition, a single coronary artery, which arose from the posterior aortic sinus, was present. Comment is made on the rarity of the occurrence of the right subclavian artery origin being proximal to a coarctation of the aorta. A review of some of the recently reported cases of the Taussig-Bing syndrome is presented.

HARVEY

Andersen, D. H., and Kelly, J.: Endocardial Fibroelastosis. 1. Endocardial Fibro-elastosis Associated with Congenital Malformations of the Heart. Pediatrics **18:** 513 (Oct.), 1956.

A very thorough and thoughtful study of fibroelastosis among the infants and children who came to autopsy at the New York Babies Hospital over a 20-year period, is presented. One hundred and ninety-nine hearts were available for analysis, of which 126 were instances of major congenital malformation. The authors state that the cases of endocardial fibroelastosis without associated malformation present a fairly uniform clinical picture, while the cases of fibrosis associated with congenital malformations present a varied clinical and pathologic picture. It seemed to the authors that the endocardial fibrosis in the latter group was secondary to varying pressures or currents in the flow of intracardiac blood caused by the malformation. All the congenital anomalies were classified, and an analysis of the sites of endocardial thickening in the types of congenital malformations was made. In considering the blood flows in these various groups, it was quite obvious to the authors that the elastosis occurred as a result of increased intracardiac pressure in a given area. The thickened valves could be reasonably ascribed to vibration, a result of eddy currents. In addition to the mechanical factors, the authors feel that partial anoxia contributes to the development of the condition. In none of the specimens was there any evidence of infection that could be considered the cause of the elastosis or the congenital malformation. An excellent review of the literature on this subject is presented.

HARVEY

Kelly, J., and Andersen, D. H.: Congenital Endocardial Fibro-elastosis. II. A Clinical and Pathologic Investigation of Those Cases without Associated Cardiac Malformations Including Report of Two Familial Instances. Pediatrics, **18:** 539 (Oct.), 1956.

These authors report further on their study of congenital endocardial fibroelastosis. In a review

of the cases of fibroelastosis at the New York Babies Hospital, 17 instances were found in which the fibroelastosis occurred without any other congenital cardiac malformation. Among these 17 cases, were 2 in which there was a familial occurrence of the disease. The symptoms and clinical course were reviewed, as well as the physical findings and pathologic findings. In general, nonspecific symptoms appeared at about 6 months of age, and these were failure to gain weight, cough, labored breathing, and tachycardia. A terminal event was usually tachycardia with vomiting. Death occurred any time after the onset of the disease, during an acute attack, or at some later date after symptoms had been present for a period of time. In all instances the pathologic findings were essentially the same; the heart was large and dilated mainly because of hypertrophy and dilatation of the left ventricle. The fibroelastosis was more common in the left ventricle, and characteristically showed an increase in the fibrous tissue beneath the endocardium with an extension of fibrous strands into the myocardium. A review of the literature was presented, as well as a hypothesis for the cause. The authors feel that the familial instance suggests that there may be some genetic metabolic defect resulting in either deficiency or abnormality of an enzyme concerned with metabolism of the myocardium and that this defect leads to the development of the fibroelastosis. They consider the familial occurrence a strong point in this hypothesis.

HARVEY

Schaede, A., Lotzkes, H., and Hilger, H. H.: Body Growth in Congenital Heart Disease. Arch. Kreislaufforsch. **24:** 1 (June), 1956.

In 576 patients with congenital heart disease diagnosed by angiocardiography and cardiac catheterization, growth was considerably retarded, especially as far as weight was concerned. This retardation was especially great in patients with large left-to-right as well as right-to-left shunts and was attributed to tissue anoxia. In aortic coarctation localized anoxia in the lower half of the body may have been responsible. Retardation of growth, as well as the decrease in life expectancy, was parallel to the degree of cyanosis, but not to the pulmonary blood flow, and was much greater in boys than in girls.

LEPESCHKIN

Caminiti, R.: The Eisenmenger Complex. II. Semiologic, Physiopathologic, and Therapeutic Aspects. Cuore e circolaz. **40:** 83 (April), 1956.

As a result of observations in 14 patients, the conclusion is reached that the most important attribute of the syndrome is pulmonary hypertension due to increased flow, and that dilatation of the pulmonary artery is secondary to this. The major factor responsible for pulmonary hypertension is the interventricular communication, and the only surgical procedure logically possible for correction of the malformation is closure of this communication.

LEPESCHKIN

CORONARY ARTERY DISEASE

Laake, H.: Interventricular Septum Infarct. Acta med. Scandinav. **153:** 193–200 (Jan. 20), 1956.

Infarction of the interventricular septum was found in 30 of 62 patients studied. The most frequent localization was anteroseptal (23 patients), whereas 5 were posteroseptal and 2 were anteroposterior and septal in location. Electrocardiographic localization was quite accurate with anteroseptal infarction but it was faulty with posteroseptal lesions. Of the 30 patients with septal infarction, 11 died. It is believed that although this mortality figure is incorrect because of the selection of cases, infarction of the septum alters the prognosis of myocardial infarction unfavorably. Of 24 cases of bundle-branch block studied with special reference to the problem of septal involvement, one half the cases were found to have recent or old infarctions of the septum on postmortem examination.

ROSENBAUM

Holton, C.: Anticoagulant Treatment in Acute Coronary Occlusion with Special Reference to Indications. Acta med. Scandinav. **155:** 14 (June 30), 1956.

A series of 166 cases of acute myocardial infarction was treated with a combination of heparin and Dicumarol as anticoagulants. The heparin was given intramuscularly in a solution containing 1.25 per cent carboxymethylcellulose. There was little discomfort and no hemorrhage at the site of injection of this material. The heparin was given until the Dicumarol began to be effective. The mortality in this series of 166 patients was 25.9 per cent. Hemorrhagic complications occurred in only 5 patients and in all of them it was mild. Hemorrhage into the myocardium occurred in 1 patient who died, but it was thought unlikely that the hemorrhage contributed to the death. There were 5 instances of thromboembolism among the 166 patients but none of these appeared at a time when the patients were believed to be under the full effect of the anticoagulant. In 22 per cent of the patients the condition of the patient changed from good to poor risk some 24 hours or more after admission. The author is of the opinion that such patients would be denied the advantages of anticoagulant therapy if the criteria of Russek were used in the selection of patients.

ROSENBAUM

Wacker, W. E. C., Ulmer, D. D., and Vallee, B. L.: Metalloenzymes and Myocardial Infarction. II. Malic and Lactic Dehydrogenase Activities and Zinc Concentrations in Serum. New England J. Med. **255:** 449 (Sept. 6), 1956.

Malic dehydrogenase activity was determined in the serum of 21 healthy adults and 7 patients with myocardial infarction. Serum lactic dehydrogenase activity was measured in 42 healthy adults, 23 patients with a variety of clinical disorders and 22 patients with acute myocardial infarction. Serum zinc was measured in 8 patients with acute infarction. Lactic dehydrogenase activity of the serum was elevated in all patients with acute myocardial infarction rising on the first day, reaching a peak on the second or third day and falling to normal by the seventh to eleventh day. The malic dehydrogenase activity followed much the same pattern and the time course and degree of elevated activity were much the same as that described for serum oxaloacetate transaminase activity. The elevations of both enzymes were 2 to 10 times those found normally. The serum zinc concentration was significantly reduced in patients with myocardial infarction, falling on the day of infarction and remaining decreased for as long as 2 weeks; this constituent of the serum is also reduced in hepatic cirrhosis and pernicious anemia. Serum lactic dehydrogenase activity was not elevated in angina pectoris, coronary insufficiency or myocardial ischemia. It did rise in renal necrosis and parenchymal liver disease, renal infarction and subacute glomerulonephritis. In some patients with myocardial infarction complications caused a secondary rise of activity and delayed the return to normal. The changes in these metalloenzymes and in the serum zinc concentration are believed to occur early enough in the disease and to be sufficiently characteristic of myocardial infarction to be valuable adjuncts in the diagnosis of that disorder.

ROSENBAUM

Wager, O., and Hällström, K.: C-Reactive Protein in Acute Coronary Disease. Cardiologia **29:** 321 (No. 5), 1956.

The occurrence of a C-reactive protein could be demonstrated in 94 per cent of 50 patients with myocardial infarction and typical electrocardiographic patterns. The positive reaction was as frequent as an elevation of the sedimentation rate and more common than leukocytosis and elevation of the temperature. It appeared before the rise of the sedimentation rate and disappeared before the latter had reached its peak levels. In cases of suspected acute coronary disease with nonspecific electrocardiographic alterations or a normal electrocardiogram, the reaction became positive only in the presence of an elevation of the sedimentation rate. The authors feel that a test for the presence of C-reactive proteins is a sensitive indicator and represents a valuable addition to other methods used to determine an active myocardial process in coronary disease.

PICK

Nezlin, V. E.: Diagnosis and Differential Diagnosis of Myocardial Infarction. Klin. Med. **34:** 10 (July), 1956.

According to the author persistence of the QS deflection in at least 4 precordial leads is suggestive of anterior ventricular aneurysm, while posterior aneurysm is characterized by persistent S-T segment elevation in leads II and III. Immediately after anterior infarction, giant positive T waves with slight S-T segment elevation may occur in the first 4 precordial leads. In the Wolff-Parkinson-White syndrome, the QS deflections in leads II and III may simulate old posterior infarction, while in chronic pulmonary disease a QS deflection localized to lead V_4 may simulate anterior infarction.

LEPESCHKIN

Smol'iannikov, A. V.: On the Pathology and Pathogenesis of Coronary Insufficiency. Klin. Med. **34:** 40 (July), 1956.

Histologic studies of the coronary arteries were made in 40 persons who died while having symptoms of coronary insufficiency and in 15 persons who died suddenly from other causes. The first group showed saturation with plasma of the walls of small arteries, hemorrhage into arteriosclerotic plaques in the larger arteries, intramural hemorrhages, stasis, and paretic dilatation of the smaller vessels. These are interpreted as due to coronary spasm, which is facilitated by the presence of arteriosclerosis. Coronary thrombosis is considered to be usually secondary to the functional spasm.

LEPESCHKIN

Luongo, E. P.: Health Habits and Heart Disease—Challenge in Preventive Medicine. J.A.M.A. **162:** 1021 (Nov. 10), 1956.

A comparsion of health habits has been made between a test group of 100 patients with manifest coronary disease and a contratest group of 200 people with the same distribution of ages and occupations but without coronary disease. Twenty-seven per cent of the test patients had average diets with a variety of foods and an apparent balance between caloric intake and energy output, while 60 per cent of the contratest group had such findings. Seventy per cent of the test gr up had no regular exercise patterns, either at work or away from it, as compared with 30 per cent of the contratest group. No influence of tobacco or alcohol was evident, but among the patients who survived coronary attacks 71 per cent had been using alcohol in moderation for from 1 to 10 years since the attack and claimed beneficial effects with less anxiety. There was evidence that the real culprits in coronary disease are not hard work, overexercise, or occupational stress, but sedentary living and poor health habits. Technologic advances are freeing more and more men from distasteful and obnoxious labor and more men will have time and money for leisure. This is

our modern challenge. We must guide men in the intelligent use of their abilities, resources, stamina, and interest in life if we would help them lead satisfying and happy existences. If we, as part of a creative minority, fail, we will find ourselves as part of a civilization unprepared for the economic riches it fought so hard to obtain.

KITCHELL

Burnett, C. F., Jr., and Evans, J. A.: Follow-Up Report on Resection of the Anginal Pathway in Thirty-three Patients. J.A.M.A. **162:** 709 (Oct. 20), 1956.

Thirty-three patients with severe disabling angina pectoris were subjected to resection of the anginal pathway. Three patients (9 per cent) died of the operative procedure. Eighteen of the surviving patients had complete relief of anginal pain for from 1 to 11 years. Eight patients were believed to have had satisfactory results, and 4 obtained no relief. Although resection of the anginal pathways is not the final answer to disabling angina pectoris, the procedure does offer relief to certain carefully selected patients. The individual with angina and hypertension in whom the procedure is combined with extensive sympathectomy and splanchnicectomy obtains the best results. The operation may offer great relief to patients with angina decubitus who have not had a recent coronary occlusion and who do not have a great functional overlay.

KITCHELL

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Toscano-Barbosa, E., Brandenburg, R. O. and Burchell, H. B.: Electrocardiographic Studies of Cases with Intracardiac Malformations of the Atrioventricular Canal. Proc. Staff Meet. Mayo Clin. **31:** 513 (Sept. 19), 1956.

The electrocardiograms in 16 patients with defects of the atrioventricular canal area, proved either at operation or post mortem, have shown a basic uniformity and may be highly distinctive in the differential diagnosis from usual types of atrial septal defect. The characteristic record shows a delayed excitation of the right ventricle of the partial right bundle-branch configuration, in general a left axis deviation and a QRS loop, as projected on the frontal plane, rotating counterclockwise, often placed superior to the isoelectric point. In some instances, a flattened, horizontally disposed figure-of-eight configuration of the QRS loop in the frontal plane may be seen. The basic pattern is modified by the presence of pulmonary hypertension and gross left ventricular enlargement caused by mitral insufficiency. The P-R interval is frequently prolonged.

SIMON

Radner, S., Linder, E., Dahlbäck, O., Edler, I., and Gustafson, A.: Suprasternal Pressure Curves in Early Mitral Stenosis. Acta Med. Scandinav. **154:** 299 (May 26), 1956.

The authors report that they have used the suprasternal puncture technic in 140 patients for hemodynamic studies. There were 68 patients with predominant mitral stenosis and, of these, 5 were considered to be in the very early stages of the disorder. The left atrial curve was characterized by a high and peaked *a* wave, believed to result from an increase in the atrial systolic force, a well-developed intrasonic dip attributed to the suction influence of the left ventricle, and an angulation on the descending limb of the second sound wave regarded as the effect of obstruction to emptying of the left atrium. The pulmonary artery wave showed a presystolic pressure rise due to retrograde transmission of the large atrial *a* wave, and a broadening of the head of the curve with a displacement of the incisure to a higher level on the catacrotic limb so that the pressure response in the pulmonary artery resembled that of the aorta. The aortic curves showed a low and narrow head, a poorly developed incisure and rebound wave; these were features that the authors have encountered in all patients with mitral valve disease and that are thought to be caused by the reduction in cardiac output.

ROSENBAUM

Bengtsson, E.: The Exercise Electrocardiogram in Healthy Children and in Comparison with Adults. Acta Med. Scandinav. **154:** 225 (May 5), 1956.

Electrocardiographic observations were made in 84 normal children and 41 normal adults at rest, in the upright position and during and after standardized heavy exercise. The exercise electrocardiogram seldom showed any significant disturbances in rhythm. The P-Q interval was not prolonged during exercise and in no case was it prolonged by more than 0.01 second above the resting value. The ventricular gradient as well as the mean electric axis of QRS tended to show a shift to the right immediately after exercise and then a shift to the left 4 minutes after exercise with T wave changes probably secondary to these axis shifts. After exercise the T waves decreased in amplitude initially and then increased in amplitude during the recovery period. When the T waves increased in amplitude, the increase was usually greater in children than in adults and when they decreased in amplitude, the fall was usually less in children. In orthostatic tests, electrocardiographic changes were less often found in children than in adults.

ROSENBAUM

AMERICAN HEART ASSOCIATION, INC.

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Remarks before the Committee on "Report of Board of Trustees and Secretary" of the American Medical Association

June 4, 1957

Edgar V. Allen, M.D., *President, American Heart Association*

Dr. Culpepper, members of the Committee, Gentlemen:

The Committee has before it a resolution introduced by the Ohio State Medical Society which would abolish voluntary health agencies and establish a National Research Fund Committee supported by Community Chests and United Funds. This matter is of such great importance that I would like to speak somewhat extensively.

First, may I identify myself. I am Dr. Edgar V. Allen, representing, in the House of Delegates of the A.M.A., the section on Experimental Medicine and Therapeutics. I have been a member of the House of Delegates for about 16 years; for a similar time I have been a member of the Board of Directors of the American Heart Association, of which I am currently President. I am a practicing internist. My interest in the American Heart Association returns no financial gain to me.

Each year about 1,700,000 Americans die. At each session of the House of Delegates of the A.M.A. we stand for a minute in silent tribute to those of our members who have died. It would be much better if, in addition, each of us would spend a day or a week annually in support of the national voluntary health agencies. For in many instances, death is not inevitable, but only an expression of medical ignorance. In addition, there are millions of Americans who are ill and who need our help. When I look into the faces of the members of our House of Delegates, I see more than a hundred who will die of cardiovascular disease. If the past is a fair sample of the future, they need not die until overcome by the infirmities of old age. I speak for those prematurely dead of cardiovascular disease, for those of us about to die and for the millions of Americans who are disabled or handicapped.

There can be no progress in the conquest of disease except as a result of research, for without research, there will be no progress! Speaking for the American Heart Association, I wish you to know that our Constitution and By-Laws state unequivocally that the acquisition of knowledge through research is our major objective. The parent organization of the American Heart Association spends 56 per cent of its funds in support of research. We are striving to raise this percentage to 70. We do not have enough money to support research adequately—we need more and better investigators, new buildings and new equipment.

If the resolution of the Ohio State Medical Association is passed by the House of Delegates a vacuum will occur. Into this vacuum will march the Federal Government. Our House of Delegates has persistently and wisely supported the concept that we want less Federal participation rather than more. Are we then to abandon a principle which we have enunciated on numerous occasions?

Time does not permit me to present in detail the ways in which the American Heart Association spends the remainder of its money, although this matter is presented publicly each year. In brief, the 44 per cent of A.H.A. funds which are not spent in support of research are spent in professional and lay education, in community services, which exclude direct patient care, and in fund raising, and administration.

We in the A.H.A. have had a great deal of experience with United appeals. Let me give you an example. In the great state of Michigan, the Michigan Heart Association received from United Funds about $500,000 annually. In my home state of Minnesota where "United Funds" constitute a minor problem, and where the population is less than half that of Michi-

gan, the people of Minnesota gave $520,000 to the Minnesota Heart Association this year. I can say with the greatest confidence that participation in single package appeals will inevitably result in smaller amounts of money for all the agencies.

My esteemed colleagues from Ohio believe that people are annoyed by multiple appeals for funds. Let us examine that belief. Hardly anyone likes to give money. I suspect that I receive as many appeals as most of you do, but they do not annoy me. The American Heart Association twists no arms and applies no "half Nelsons" to raise funds. I lament that I cannot give to all appeals, but in keeping with the American way of life I can decide to which organizations I shall contribute.

Accepting for the moment that there is annoyance in some geographic areas, may I ask some questions? Does a physician lock the door of his office because some patients annoy him? Would you destroy a highway because you are annoyed by the heavy traffic? Does one throw his monthly bills into the waste basket because they annoy him?

I am told there is a ground swell of opinion against voluntary health agencies. Mr. Chairman, and members of the Committee: that ground swell grows to alarming proportions only in geographic areas where physicians and lay people fail to furnish appropriate leadership in voluntary health agencies. This is not a new ground swell of opinion. We have contended with it every year since the American Heart Association became a national voluntary health agency in 1948. Yet, in spite of it, we have grown every year.

I am told that in Ohio the newspapers favor United Funds. In Minnesota and in many other areas they do not. But if they do, are the newspapers always right? Do they express a cross-section of American opinion? I remember the Literary Digest. It was wrong—it is gone. I remember that in 1948 the newspapers, for the most part, supported the losing candidate for the Presidency of the United States. In the years in which I have been in the House of Delegates of the American Medical Association I have often heard the words "liberty" and "free choice of physician." Can our body support the concept of free choice of physician and deny free choice in giving?

My colleagues in Ohio seem to have a difficult problem. Can they solve that problem by forcing us in Minnesota, and in other areas, to accept a philosophy which we deny and which is foreign to our own philosophy? Are we to say that every state must submit to a system which it does not wish because one state, or a few states, have problems?

It has been said to me that some voluntary health agencies have an entrenched and expensive bureaucracy. I have never been able to get the details about this situation but even presuming it is true, shall we penalize all voluntary health agencies for the misdeeds of a few? It is no news to you that in many quarters, the American Medical Association is held to be an intolerable and undesirable organization. Shall we abolish the American Medical Association? Shall we destroy every horse at whose heels a dog barks?

I have been told that many voluntary health agencies have $30,000 a year men. In the American Heart Association we pay no one as much as $30,000 a year. Last year I spent a great many days at medical meetings, largely in the interests of the American Heart Association. I received no pay. There are hundreds, yes thousands of volunteers who work without pay, and without recompense except the comforting belief that they have contributed to a worthy cause. It has been said that people have rebelled against voluntary health agencies, yet this year on Heart Sunday, one million volunteers were on duty. In 1956 there were only 750,000 volunteers on Heart Sunday. Do these figures represent rebellion?

My colleagues from Ohio have indicated that research funds should be administered by physicians. Gentlemen, they desire something which already has been accomplished in the A.H.A. All of our research funds are administered by physicians.

The resolution of the Ohio State Medical Society presents us with a wholly unacceptable proposition, a proposition that the opinions of a few should govern the activities of the many. I have heard no support from any other State Medical Society for the resolution from the Ohio State Medical Society. Surely that resolu-

tion is contrary to the American way of life and the expressed policies of the A.M.A. House of Delegates.

The A.H.A. is ready and willing to consider common problems with other voluntary health agencies and any responsible committee of the A.M.A. such as that already established for this purpose by the Board of Trustees of the A.M.A. The A.H.A. does not claim perfection, although it strives for it. However, the A.H.A. does not believe that this committee should report favorably on the resolution of the Ohio State Medical Society, to the House of Delegates. Certainly this is not the time for precipitous action.

Much has been said in the A.M.A. House of Delegates about the interposition of a third agency between the patient and the physician. We, in the A.M.A. have fought this concept vigorously. Can we then, in good conscience, place the A.M.A. or a United Health Fund between the voluntary health agencies and the American people?

Finally let me say that two presidents have expressed to me personally their support of voluntary health agencies—Dwight Eisenhower, President of the United States and Dwight Murray, President of the A.M.A.

May I reiterate—the A.H.A. and, I believe, other voluntary health agencies are trying to preserve life and health. Shall we destroy this good by taking an easy path or shall we, imbued with unyielding determination, pursue the path which has produced results in the past and which gives great promise for the future?

Dr. Culpepper, members of the Committee: I strongly urge that you recommend no action on the Ohio State Medical Association resolution to the House of Delegates. I respectfully suggest that it be referred to the Committee already established by the Board of Trustees for this purpose. In this Committee, leisurely and definitive consideration can be given to a multitude of vexatious problems. Gentlemen of the Committee, we must not err in this most important matter!

After the first link, the chains of tyranny forge themselves. We of the A.M.A. wish no first link.

ANNUAL MEETING AND SCIENTIFIC SESSIONS

A listing of the titles and authors of papers to be presented at the 30th Scientific Sessions of the Association will be found on pages 681-685 Information about medical films, technical and scientific exhibits and other features is included on pages 686-694.

The Scientific Sessions, which will commemorate the tercentenary of the death of William Harvey, are part of the Association's 33rd Annual Meeting. The entire program, at the Hotel Sherman in Chicago, will extend from Friday, October 25, through Tuesday, October 29.

The opening day's events will include a number of special features. For the first time, there will be an all-day teaching program for physicians in general medicine. This program, devoted to the subject of "Prevention and Management of Cardiovascular Emergencies," has been classified by the American Academy of General Practice as acceptable for Category II credit for Academy members. There will also be an all-day Symposium on Heart Sounds and Murmurs. Another special session on "Instrumental Methods in Cardiovascular Diagnosis" is scheduled for Friday evening.

The regular Scientific Sessions will get under way on Saturday morning, October 26 and will end Monday noon, October 28. A total of 82 papers has been selected by the Program Committee out of 285 submitted for consideration. Abstracts of papers submitted will be published in the November Circulation.

The five-day program will be attended by thousands of physicians, research scientists, lay leaders and others who are active in organizational affairs and community service activities of Heart Associations.

The following program highlights include features not listed elsewhere in this issue.

Friday, October 25

7:00 P.M. Staff Conference of Heart Associations, dinner address by Robert W. Wilkins, M.D., Boston, the Association's President-Elect.

Saturday, October 26

9:00 A.M. AHA President Edgar V. Allen, M.D., Rochester, Minn., opens the Scientific Sessions

with a brief address honoring William Harvey. Dr. Allen will present Citations For Distinguished Research Achievement to Andre F. Cournand, M.D. and Dickinson W. Richards, Jr., M.D., both of New York.

12:30 P.M. Luncheon and business meeting of the Association's Council on Rheumatic Fever and Congenital Heart Disease.

Sunday, October 27

12:30 P.M. Luncheon and business meeting of the Council on Community Service and Education.

7:00 P.M. Annual Dinner of the American Heart Association. Presentation of Gold Heart Awards Dinner dance.

Monday, October 28

9:30 A.M. Assembly convenes. Keynote address by Brig. Gen. Philip P. Ardery, Louisville, Ky.

10:00 A.M.–5 P.M. Assembly Panel Discussions.

1:00 P.M. Assembly luncheon, address by President Allen.

7:00 P.M. Dinner for Presidents and Board Chairmen of Heart Associations. Address by Howard B. Sprague, M.D., Boston, Past President, AHA.

Tuesday, October 29

9:30–Noon General meeting of Assembly. Presentation and discussion of panel reports. Election of officers and board members. Installation of Robert W. Wilkins, M.D., Boston, as President.

12:30 P.M. Staff Conference of Heart Association, business luncheon.

Registration

Advance registration forms for the Annual Meeting and the Scientific Sessions may be obtained from the Association. In order to pick up programs and other materials, those who have registered as well as new registrants are required to check at the registration desk, which will be maintained at the Hotel Sherman from Friday 8 A.M., October 25, through Tuesday noon, October 29.

Hospitality Booth

The Chicago Heart Association will maintain a Hospitality Booth at the Hotel Sherman. The booth will provide information on restaurant, recreational, educational and shopping facilities of Chicago. Special attractions arranged for wives of participants include visits to the Chicago Art Institute, a tour of the city and a fashion show and tea at a leading department store

Non-Members Welcome

Attendance at the Scientific Sessions is open to non-members as well as to Heart Association members. A $3.00 registration fee will be charged to non-members. This charge will entitle them to copies of the printed abstracts. Medical students, interns, residents, research workers and nurses will be welcome without payment of the fee.

NOVEMBER 1 DEADLINE FOR GRANTS-IN-AID APPLICATIONS

November 1 is the deadline for submitting applications for grants-in-aid to be awarded by the Association for the fiscal year beginning July 1, 1958.

Full information and application blanks may be obtained from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N. Y. Applications for investigatorships and fellowships for the same period were due last September 15.

THIRD WORLD CONGRESS OF CARDIOLOGY

President: Professor P. Rylant, Brussels.
Secretary: Dr. F. Van Dooren, 80, rue Mercelis, Brussels, Belgium.

The Third World Congress of Cardiology will be held in Brussels, Belgium, from September 14 to 21, 1958.

Registration is open to members of the various national societies and associations engaged in the study and control of cardiovascular disease and to physicians and scientists who reside in countries where no national society of cardiology has as yet been established.

The Organizing Committee of the Third World Congress will send to every American physician who attended the Second World Congress in Washington (1954) the pamphlet on the Third World Congress and application forms. Cardiologists in the United States who did not attend the Second World Congress but who wish to have more information on the forthcoming Congress in Brussels (1958) may write to the American Heart Association.

Scientific Agenda

The Scientific Agenda will consist of:

1. *General Sessions*

2. *Symposia* devoted to the following subjects: Physiology of the Cardiovascular System, Cardiac Insufficiency, Peripheral Vascular Circulation, Physiology and Pathology of Coronary Circulation, Pulmonary Circulation, Relationship between Anatomical Changes and Electrocardiographic Patterns, Normal Limits and Functional Changes of the Electrocardiogram, Radiological Methods, Epidemiology

and Social Aspects of Cardiovascular Disease, Arteriosclerosis, Hypertension, Collagen Diseases, Congenital and Rheumatic Heart Disease.

3. *Panel discussions* of the following subjects: Surgery for congenital and acquired cardiovascular disease, pulmonary heart disease, cardiac insufficiency, angina pectoris, rheumatic fever, minor alterations of the electrocardiogram, acute endocarditis, peripheral blood circulation, pulmonary function with mitral stenosis, angiocardiography, phonocardiography. Participants in symposia and panel discussions have been invited by the Scientific Committee of the Congress.

4. *Scientific papers.* These will be limited to 10 minutes.

5. *Clinico-Pathological Conferences.*

6. *Medical Films.*

7. *Scientific and technical exhibits.*

8. *Special meetings.*

9. Presentation of the Award of the Belgian Society of Cardiology.

Members of the Congress who wish to present a paper should send a 200-word typewritten summary in English and a translation in French, Spanish *or* German to the Secretary of their national society of cardiology *before the first of February 1958.* (Authors in the United States will send their abstracts to the American Heart Association.) Participants residing in a country which has no National Society of Cardiology should address their abstract and translation directly to the Secretary of the Congress, who will submit it to the Scientific Committee. No participant should present more than one paper. Papers may be given in English, French, Spanish or German.

Congress Fees

Active members: 1500 Belgian Francs. This fee includes admission to all scientific sessions, printed abstracts of the papers, the badge, and participation in all social events including the banquet.

Associate members (wives and families of Congress members): 1000 Belgian Francs. This fee includes all privileges of the active members except the printed abstracts.

ALBERT EINSTEIN MEDICAL CENTER SCHEDULES COURSE IN ELECTROCARDIOGRAPHY

The Albert Einstein Medical Center will conduct a Post Graduate course in advanced electrocardiography at the Southern Division, Fifth and Reed Streets, Philadelphia, beginning February 19, 1958. The course will consist of a total of 30 hours of instruction divided into 10 sessions to be held on consecutive Wednesdays from 2 to 5 P.M. The fee for the course is $50.00.

COMPLEX ARRHYTHMIAS SUBJECT OF MICHAEL REESE HOSPITAL COURSE

An advanced course for experienced electrocardiographers in the interpretation of complex arrhythmias will be given at Chicago's Michael Reese Hospital by Louis N. Katz, M.D., Richard Langendorf, M.D., and Alfred Pick, M.D. Classes will meet daily from 9 AM to 5 PM, December 9–13, 1957. A copy of the lecture schedule may be obtained from the secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

CHICAGO HOSPITAL OFFERS RESIDENCY IN CARDIOLOGY

The Mount Sinai Hospital in Chicago offers a one-year approved residency in cardiology. The training is integrated with that of the Division of Cardiology of the Chicago Medical School.

Applicants should have completed a three-year residency in medicine, or a two-year residency in medicine or pediatrics, plus one year in cardiology.

Inquiries should be addressed to Aldo A. Luisada, M.D., Director, Division of Cardiology, 2755 West 15th Street, Chicago 8, Ill.

MEETINGS CALENDAR

October 25–28: Scientific Sessions of the American Heart Association. Chicago. American Heart Association, 44 East 23rd Street, New York 10, N. Y.

October 31: American Federation of Clinical Research, Midwestern Section, Chicago. Robert P. Gilbert, M.D., Evanston Hospital, Evanston, Ill.

November 3–4: American Society for the Study of

Arteriosclerosis, Chicago, Ill. O. J. Pollak, M.D., P.O. Box #228, Dover, Del.

November 11–15: American Public Health Association, Cleveland. R. M. Atwater, M.D., 1790 Broadway, New York 19, N. Y.

November 16: American School Health Association, Cleveland. A. O. DeWeese, 515 E. Main Street, Kent, Ohio.

November 17–22: Radiological Society of North America, Chicago. D. S. Childs, M.D., 713 E. Genesee Street, Syracuse 2, N. Y.

November 22–23: Council for High Blood Pressure Research of the American Heart Association, Cleveland. Mrs. Jerry H. Bruner, 1689 East 115th Street, Cleveland 6, Ohio.

December 3–6: American Medical Association, Philadelphia. George F. Lull, 535 N. Dearborn Street, Chicago 10, Ill.

December 6–7: American Federation for Clinical Research, Eastern Section, New Haven, Conn. Franklin H. Epstein, M.D., Department of Internal Medicine, Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.

January 24, 1958: American Federation of Clinical Research, Southern Section, New Orleans, La. Kenneth R. Crispell, M.D., Department of Internal Medicine, University Hospital, Charlottesville, Va.

January 29–30: American Federation for Clinical Research, Western Section, Carmel, Calif. Monte A. Greer, M.D., University of Oregon Medical School, Portland, Ore.

ABROAD

September 14–21, 1958: Third World Congress of Cardiology, Brussels, Dr. F. Van Dooren, 80 rue Mercelis, Brussels, Belgium.

30th SCIENTIFIC SESSIONS

of the AMERICAN HEART ASSOCIATION

Commemorating the Tercentenary of William Harvey

October 25–28, 1957

ROBERT W. WILKINS, M.D.

As President-elect of the American Heart Association, Dr. Robert Wallace Wilkins climaxes a distinguished career as clinician, teacher and regional and national leader in the Heart organization. He is Professor of Medicine at the Boston University School of Medicine and serves as Associate Director, Evans Memorial Hospital and as Associate Physician-in-Chief, Massachusetts Memorial Hospitals, both in Boston.

Dr. Wilkins was the first physician in the Western world to employ the ancient Indian snakeroot, rauwolfia, and its derivative, reserpine, in the treatment of high blood pressure. The drug is now widely used for this purpose and as a tranquilizer. During World War II, he did research on aviation medicine, and developed the net "G" suit, a pressure suit for high altitude aviators, and a parachute and harness.

Since 1953, Dr. Wilkins has served as Vice President of the American Heart Association and during 1954–56 he was President of the Massachusetts Heart Association. From 1949–50, he served as Vice Chairman of the American Foundation for High Blood Pressure. Since that time the Foundation has been merged with the American Heart Association as its Council for High Blood Pressure Research. He served as Chairman of the Council's Medical Advisory Board during 1950–51.

Dr. Edgar V. Allen, completing his term as President of the American Heart Association, has been a leader in the medical and organizational affairs of the Association since the years when it was purely a professional society of physicians. He has been Chairman of the Association's Section on Peripheral Circulation, member of the Board of Directors and its Executive Committee, and a Vice President.

Dr. Allen's teaching career at the Mayo Foundation spans three decades and has been paralleled by an equally outstanding clinical career. He was appointed Chief of a section in the Division of Medicine at the Mayo Clinic in 1935, and was made Senior Consultant in Medicine in 1947.

Dr. Allen was Governor of the American College of Physicians for Minnesota and was respectively Councilor, Vice President and President of the Central Society for Clinical Research. He served for many years as a member of the Subcommittee on Cardiovascular Diseases of the National Research Council. A member of the House of Delegates of the American Medical Association since 1941, he has been Chairman of the A.M.A.'s Committee on Distinguished Service Awards and of its Association of Section Delegates.

EDGAR V. ALLEN, M.D.

30th SCIENTIFIC SESSIONS

of the AMERICAN HEART ASSOCIATION

Commemorating the Tercentenary of William Harvey

October 25–28, 1957

FRIDAY
OCTOBER 25, 1957

SPECIAL SCIENTIFIC SESSION FOR PHYSICIANS IN GENERAL MEDICINE

Bal Tabarin Room—9:00 A.M. to 12:30 P.M.
—2:00 P.M. to 5:00 P.M.

Chairman: **Howard B. Sprague, Boston, Mass.**

MORNING

Prevention and Management of Cardiovascular Emergencies

...In Pregnancy, *James Metcalfe, Boston, Mass.*
...In Children, *Benjamin M. Gasul, Chicago, Ill.*
...During Anesthesia, *Robert A. Hingson, Jr., Cleveland, Ohio.*

INTERMISSION

...After Surgery, *Louis A. Soloff, Philadelphia, Pa.*
...During Drug Therapy, *Maurice Sokolow, San Francisco, Calif.*
...In Anxiety States, *Stewart G. Wolf, Jr., Oklahoma City, Okla.*

AFTERNOON

PANEL: Prevention and Management of Cardiovascular Emergencies

(Panel presentation to be followed by questions and discussion from the floor)

HOWARD B. SPRAGUE, *Boston, Mass. MODERATOR*
SPEAKERS OF THE MORNING SESSION

INTERMISSION

PANEL: Unsettled Clinical Questions in the Management of Cardiovascular Disease

LOUIS N. KATZ, *Chicago, Ill., MODERATOR.*
GEORGE E. BURCH, *New Orleans, La.*
ALBERT DORFMAN, *Chicago, Ill.*
A. CARLTON ERNSTENE, *Cleveland, Ohio.*
HANS H. HECHT, *Salt Lake City, Utah.*
ROBERT L. PARKER, *Rochester, Minn.*

Symposium on Heart Sounds and Murmurs

Parlors H & J—9:00 A.M. to 5:00 P.M.

Chairman: **Victor McKusick, Baltimore, Md.**

Instrumental Methods in Cardiovascular Diagnosis

Ballroom—8:00 P.M. to 11 P.M.

Chairman: **Charles E. Kossmann, New York, N. Y.**

Co-chairman: **Jeremiah Stamler, Chicago, Ill.**

Left Atrial Electrokymography in Mitral Insufficiency in Man: Correlative Study by Angiocardiography, Left Heart Catheterization, and Experimental Production in Dogs. *Richard D. Judge, Melvin M. Figley, and Herbert E. Sloan, Jr., Ann Arbor, Mich.*

Use of Coronary Arteriography in Human Coronary Sclerosis. *Alan P. Thal, Richard G. Lester, L. Stephen Richards, and M. John Murray, Minneapolis, Minn.*

Use of a New Sagittal Lead for Estimation of Ventricular Hypertrophy. *Ernest W. Reynolds, Jr., and Franklin D. Johnston, Ann Arbor, Mich.*

Critical Study of Existing Electrocardiographic

Lead Systems to Evolve One Useful Interchangeably for Scalar, Vector, and Electronic Computer Analysis. *Ernst Simonson and Otto H. Schmitt, Minneapolis, Minn.*

Critical Evaluation of the Equivalent Cardiac Dipole Concept. *Ralph F. Morton and Daniel A. Brody, Memphis, Tenn.*

INTERMISSION

Clinical Application of a New Dye for Continuous Recording of Arterial Dilution Curves Independently of Variations in Blood Oxygen Saturation. *Irwin J. Fox, Rochester, Minn., Leslie G. Brooker, Donald W. Heseltine, Rochester, N. Y., and Earl H. Wood, Rochester, Minn.*

Place of Intracardiac Phonocardiography in the Diagnosis of Heart Disease in Man. *George W. Deitz, Ali Ertugrul, Philadelphia, Pa., John D. Wallace, James R. Brown, Jr., Johnsville, Pa., and David H. Lewis, Philadelphia, Pa.*

High Sensitivity Pickup for Cardiovascular Sounds. *Dale Groom, Charleston, S. C., and Yro T. Sihvonen, Detroit, Mich.*

Instantaneous Measurement of Oxygen Saturation at Cardiac Catheterization, Using Reflected Light. *W. G. Zijlstra, G. A. Mook, Groningen, The Netherlands, and A. S. Nadas, Boston, Mass.*

Cinefluorography of the Heart and Lungs. *Robert S. Green, Cincinnati, Ohio.*

SATURDAY MORNING OCTOBER 26, 1957

GENERAL SCIENTIFIC SESSION

Ballroom—9:00 A.M. to 12:30 P.M.

Chairman: **Edgar V. Allen, Rochester, Minn.**

Co-chairman: **George E. Burch, New Orleans, La.**

OPENING ADDRESS: EDGAR V. ALLEN
SPECIAL AWARDS PRESENTATION

Screening Test for Renal and Adrenal Forms of Hypertension, Based upon Postural Change in Blood Pressure. *Reginald H. Smithwick, Dera Kinsey, and George P. Whitelaw, Boston, Mass.*

Diagnostic Applications of Indicator Dilution Technics in Congenital and Acquired Heart Disease. *H. J. C. Swan and Earl H. Wood, Rochester, Minn.*

Blood Pressure in White People Over 65 Years of Age. *Arthur M. Master, Richard P. Lasser, and Harry L. Jaffe, New York, N. Y.*

Study of the Manifestations of Rheumatic Fever Following Cessation of Therapy. *Edward E. Fischel, Charles W. Frank, and Marjorie T. Bellows, New York, N. Y.*

Comparison of Oral Penicillin and Oral Sulfadiazine in Controlled Study of Three Methods of Prophylaxis Against Streptococcal Infection in Population of Rheumatic Children. *Harrison F. Wood, Alvan R. Feinstein, Ilse Hirschfeld, Rita Simpson, Angelo Taranta, Raymond C. Haas, Konrad Ulich, Carlos Manso, Arthur J. Lewis, Jeanne A. Epstein, and Lawrence Rothfield, Irvington-on-Hudson, N. Y.*

Late Hemodynamic Complications of Anastomotic Procedures for Cyanotic Congenital Heart Disease. *Richard S. Ross, Melvin H. Evans, and Helen B. Taussig, Baltimore, Md.*

INTERMISSION

THE LEWIS A. CONNER MEMORIAL LECTURE:

Rheumatic Heart Disease—A Challenge.
Charles H. Rammelkamp, Jr., Cleveland, Ohio

SATURDAY AFTERNOON OCTOBER 26, 1957

SIMULTANEOUS SCIENTIFIC SESSIONS

Basic Science*

Bal Tabarin Room—2:00 P.M. to 5:00 P.M.

Chairman: **Eric Ogden, Columbus, Ohio**

Co-Chairman: **James W. McCubbin, Cleveland, Ohio**

Radioactive Fat Absorption Patterns: Significance in Coronary Artery Atherosclerosis. *William Likoff, Donald Berkowitz, Asher Woldow, and Gerson Jacobs, Philadelphia, Pa.*

Function of the A-V Conduction Tissue. *Allen M. Scher, Juhan Liikane, Malcolm E. Fishback, and Leland L. Burnett, Seattle, Wash.*

Coronary Flow and Oxygen Metabolism. *Louis N. Katz, Harold Feinberg, and Augusto Gerola, Chicago, Ill.*

Effect of Alteration of Coronary Perfusion Pressure on the Oxygen Uptake of the Left Myocardium. *Donald E. Gregg, Claudia R. Rayford, Edward M. Khouri, Albert A. Kattus, and William P. McKeever, Washington, D. C.*

Dynamics of Coronary Collateral Flow in the Normal Open Chest Dog. *Albert A. Kattus and Donald E. Gregg, Washington, D. C.*

* *Note:* Joint all-day session by the Microcirculatory Conference and the Council on Basic Science, Friday, October 25, 1957.

INTERMISSION

Production of Experimental Myocardial Failure by Coronary Artery Embolization. *Emanuel Marcus, Louis N. Katz, Ruth Pick, and Jeremiah Stamler, Chicago, Ill.*

On Computing Cardiac Work. *Carl R. Honig, Rochester, N. Y., and Stephen M. Tenney, Hanover, N. H.*

Pulmonary Vascular Responses to Serotonin and the Effects of Certain Serotonin Antagonists. *John C. Rose, Washington, D. C.*

Cardiac Control in Intact Dogs. *Robert F. Rushmer, Dean L. Franklin, Robert W. Moss, and Allan W. Lobb, Seattle, Wash.*

Circulation

Louis XVI Room—Business Meeting 1:30 P.M. —Sessions 2:00 P.M. to 5:00 P.M.

Chairman: **Herbert Chasis, New York, N. Y.**

Co-Chairman: **Milton Mendlowitz, New York, N. Y.**

Measurement of Cardiac Output in the Steady State by the Fick Principle During Combined Right and Left Heart Catheterization. *Philip Samet, William H. Bernstein, Robert S. Litwak, Hyman Turkewitz, and Leonard Silverman, Miami Beach, Fla.*

Hemodynamic Reactions to Endotoxin. *Robert P. Gilbert, Chicago, Ill., Hiroshi Kuida, Salt Lake City, Utah, Lerner B. Hinshaw, James Vick, and Maurice B. Visscher, Minneapolis, Minn.*

Method for Detection and Estimation of Magnitude of Aortic Regurgitant Flow. *Eugene Braunwald and Andrew G. Morrow, Bethesda, Md.*

Chlorothiazide in Management of Edema of Heart Failure, Nephrosis and Cirrhosis. *John H. Laragh and Felix E. Demartini, New York, N. Y.*

Hemodynamic Effects of Vasodilatation Induced by Sodium Nitrite in Congestive Heart Failure: Relationship to Starling's Law of the Heart. *Albert M. Ziffer, Bertha Rader, and Ludwig W. Eichna, New York, N. Y.*

INTERMISSION

Electrolyte and Water Metabolism in Cardiac Patients with Early Congestive Heart Failure. *Adam V. Chobanian, Belton A. Burrows, and William Hollander, Boston, Mass.*

Splanchnic Blood Volume in Congestive Heart Failure. *Elliot Rapaport, San Francisco, Calif., Myron H. Weisbart, and Milton LeVine, Albany, N. Y.*

Abnormalities of Blood Distribution in Congestive Heart Failure. *William R. Milnor and Lucien A. Campeau, Baltimore, Md.*

Comparative Cardiac Effects of Various Sympathomimetic Amines. *James W. West, Santiago V. Guzman, and Samuel Bellet, Philadelphia, Pa.*

Clinical Cardiology

Ballroom—2:00 P.M. to 5:00 P.M.

Chairman: **William P. Thompson, Los Angeles, Calif.**

Co-Chairman: **Wright R. Adams, Chicago, Ill.**

Correlative Study of Postmortem, Electrocardiographic and Spatial Vectorcardiographic Data in Myocardial Infarction. *George E. Burch, Leo Horan, Joseph Ziskind, and James Cronvich, New Orleans, La.*

Role of Electrolytes in the Origin of Ischemic Cardiac Pain and Associated Electrocardiographic Abnormalities. *Richard S. Gubner and Donald J. Behr, New York, N. Y.*

Electrocardiographic Syndrome of Short P-R Interval and Broad QRS Complexes: Clinical Study of 80 Cases. *Milton R. Hejtmancik and George R. Herrmann, Galveston, Tex.*

Uncommon Types of Cardiovascular Disease Associated with Free Aortic Regurgitation into the Heart. *Oglesby Paul, John S. Graettinger, and Arnold Brown, Chicago, Ill.*

Backflow in the Aorta of Patients with Aortic Insufficiency Studied with an Indicator Technic. *Homer R. Warner and Alan F. Toronto, Salt Lake City, Utah.*

INTERMISSION

Observations on the Significance of the Delayed Appearance of the First Heart Sound in Mitral Stenosis. *James J. Leonard, Arnold M. Weissler, and James V. Warren, Durham, N. C.*

Comparison between Electrokymograms of Left Atrium and Left Atrial Pressure Patterns in Lesions of the Mitral Valve. *Chi K. Liu and Aldo A. Luisada, Chicago, Ill.*

Cardiac Effects of Sympathomimetic Amines in Experimental Complete Heart Block. *Arthur J. Linenthal, Paul M. Zoll, Leona R. Norman, William Gibson, and Hussein A. Shustari, Boston, Mass.*

Enhancement and Inhibition of Diuresis in Congestive Heart Failure. *Stanley L. Kass, Jacob Grossman, Raymond E. Weston, and Louis Leiter, New York, N. Y.*

Rheumatic Fever and Congenital Heart Disease

Assembly Room—Business Meeting 1:30 P.M.
G. B. Shaw Room—Session 2:00 P.M. to 5:00 P.M.

Chairman: **Maclyn McCarty, New York, N. Y.**

Co-Chairman: **Jesse E. Edwards, Rochester, Minn.**

Early Postoperative Results Following Partial Correction of Transposition of the Great

Vessels. *Robert A. Miller and Thomas G. Baffes, Chicago, Ill.*

Regression after Open Valvotomy of Infundibular Stenosis Accompanying Severe Valvular Pulmonic Stenosis. *Mary Allen Engle, George R. Holswade, Henry P. Goldberg, and Frank Glenn, New York, N. Y.*

Rapid Measurement of the $_pCO_2$ of the Pulmonary Artery in Man: Clinical Use in Diagnosis of Congenital Heart Disease in 75 Patients. *John J. Osborn, San Francisco, Calif.*

Pulmonary Diffusing Capacity in Valvular and Congenital Heart Disease. *J. Howland Auchincloss, Jr., Robert Gilbert, and Robert H. Eich, Syracuse, N. Y.*

Use of Nitrous Oxide in a New and Improved Method for Detection of Left-to-Right Shunts. *Richard J. Sanders, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.*

INTERMISSION

Localization of Intracardiac Shunts by Two-Site Sampling. *Milton G. Crane, John E. Holloway, Charles H. Sears, James A. McEachen, Ronald H. Selvester, and Ivor C. Woodward, Los Angeles, Calif.*

Hemodynamic Observations in 23 Patients with Pure Mitral Insufficiency. *John Ross, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.*

Left Heart Angiography in the Diagnosis of Mitral or Aortic Insufficiency. *Robert J. Wilder, Baltimore, Md. and Howard L. Moscovitz, New York, N. Y.*

Simple Method Using Indicator-Dilution Curves to Differentiate Patients with Predominant Mitral Stenosis from Those with Predominant Regurgitation. *Edward Woodward, Jr., Howard B. Burchell, and Earl H. Wood, Rochester, Minn.*

SUNDAY MORNING OCTOBER 27, 1957

GENERAL SCIENTIFIC SESSION

Ballroom—9:00 A.M. to 12:30 P.M.

Chairman: **Irvine H. Page, Cleveland, Ohio**

Co-Chairman: **Edgar A. Hines, Rochester, Minn.**

Direct Experimental Approaches to Problem of Intraventricular Diastolic Suction. *Gerhard A. Brecher and Abbott T. Kissen, Columbus, Ohio.*

Ventilatory Mechanics in Pulmonary Edema in Man. *John T. Sharp, Geraint T. Griffith, Ivan L. Bunnell, and David G. Greene, Buffalo, N. Y.*

Circulation and Respiration in the Giraffe. *James V. Warren, Durham, N. C., John L. Patterson, Jr., Richmond, Va., Joseph T. Doyle, Albany, N. Y., Otto H. Gauer, Bad Nauheim, Germany, E. N. Keen, Capetown, S. Africa, Maurice McGregor, Johannesburg, S. Africa, and Robert H. Goetz, Capetown, S. Africa.*

Influence of Acidosis on Cardiac and Vascular Responsiveness to Epinephrine, Norepinephrine, and Metaraminol. *Max H. Weil, Duarte, Calif., Dudley B. Houle, E. B. Brown, Jr., Gilbert S. Campbell, Minneapolis, Minn., and Charles Heath, Edmonton, Alberta, Canada.*

Increasing Incidence of Liver Necrosis: Possible Relationship to Administration of Vasopressor Amines. *Philip L. Eckman, Joel G. Brunson, and John B. Campbell, Minneapolis, Minn.*

INTERMISSION

Differentiation of Types of Idiopathic Hypercholesteremia by Serum Lipoprotein Distribution and Response to Therapy. *Edwin Bowie, Jr., and Henry M. McLaughlin, Charleston, S. C.*

Changes in the Serum Cholesterol and Blood Clotting Time in Men Subjected to Cyclic Variation of Emotional Stress. *Ray H. Rosenman and Meyer Friedman, San Francisco, Calif.*

THE GEORGE E. BROWN MEMORIAL LECTURE:

Current Evaluation of the Thrombosis Problem *Nelson W. Barker, Rochester, Minn.*

SUNDAY AFTERNOON OCTOBER 27, 1957

GENERAL SCIENTIFIC SESSION

Ballroom—2:00 P.M. to 5 P.M.

Chairman: **Robert W. Wilkins, Boston, Mass.**

Co-Chairman: **Harold Feil, Cleveland, Ohio**

PRESENTATION OF THE ALBERT LASKER AWARD

Effect of Certain Unsaturated Fatty Acids on Serum Lipids. *Martin M. Nothman, Lowell Bellin, and Samuel Proger, Boston, Mass.*

Comparison of the Effects of β-Sitosterol and Safflower Oil, Alone and in Combination, on Serum Lipids of Humans: Long-Term Study. *John W. Farquhar and Maurice Sokolow, San Francisco, Calif.*

PANEL: Present Status of Lipid Metabolism and Atherosclerosis

HERBERT POLLACK, *New York, N. Y., MODERATOR*
ROBERT OLSON, *Pittsburgh, Pa.*
OGLESBY PAUL, *Chicago, Ill.*
HERMAN E. HILLEBOE, *Albany, N. Y.*

INTERMISSION

Water Metabolism after Cardiac Operations Involving Extracorporeal Circulation. *George S. Sturtz, John W. Kirklin, Edmund C. Burke, and Marschelle H. Power, Rochester, Minn.*

Phonocardiogram in Mitral Valvular Disease: Correlation with Left Heart Catheterization and Operative Findings. *Munro H. Proctor, Boston, Mass., Rhett P. Walker, Mobile, Ala., Ernest W. Hancock and Walter H. Abelmann, Boston, Mass.*

Posteromedial Annuloplasty—Correction of Acquired Mitral Insufficiency Under Direct Vision, Utilizing a Pump-Oxygenator: Clinical Experience. *K. Alvin Merendino, John E. Jesseph, Paul W. Herron, George I. Thomas, and Roy R. Vetto, Seattle, Wash.*

Physiologic Changes with Age in Ventricular Septal Defect. *Paul Adams, Ray C. Anderson, Peter Allen, and C. Walton Lillehei, Minneapolis, Minn.*

Council on Community Service and Education

Assembly Room—3:30-5:00 P.M.

PANEL: Community Service—Its Nature and Its Significance for Heart Associations

RAY E. TRUSSELL, *New York, N. Y., MODERATOR*
DEAN K. CRYSTAL, *Seattle, Wash.*
JOHN BRUNDAGE, *Montclair, N. J.*
HELEN O'SHAUGHNESSEY, *New York, N. Y.*
STEWART G. WOLF, JR., *Oklahoma City, Okla.*

MONDAY MORNING OCTOBER 28, 1957

SIMULTANEOUS SCIENTIFIC SESSIONS

Cardiovascular Surgery

Bal Tabarin Room—9:00 A.M. to 12:30 P.M.

Chairman: **Frank Glenn, New York, N. Y.**
Co-Chairman: **John H. Gibbon, Jr., Philadelphia, Pa.**

Experimental and Clinical Results with a Practical Membrane Blood Oxygenator. *George H. A. Clowes, Jr., and William E. Neville, Cleveland, Ohio.*

Postoperative Sequelae with the Bubble Dispersion Type Oxygenator: Antifoam Toxicity. *William A. Reed and C. Frederick Kittle, Kansas City, Kan.*

Use of the Heart-Lung Pump for Direct Surgical Repair of Atrioseptal Defects. *Alvin A. Bakst, Philip Crastnopol, and Irving G. Kroop, Brooklyn, N. Y.*

Plasma Concentrations of Epinephrine and Arterenol During Cardiopulmonary Bypass. *Eugene F. Woods, James A. Richardson, William H. Lee, Jr., John D. Ashmore, and Edward F. Parker, Charleston, S. C.*

Disposable Screen Oxygenator. *Gerald A. Diettert and Bernard A. Bercu, St. Louis, Mo.*

INTERMISSION

Surgical Correction of Chronic Mitral Insufficiency in Dogs. *Sam J. Kuykendall, F. Henry Ellis, Jr., and John H. Grindlay, Rochester, Minn.*

Coronary and Peripheral Blood-Flow Following Hemorrhagic Shock, Transfusion, and Norepinephrine. *Keith D. J. Vowles, Cecil M. Couves, and John M. Howard, Atlanta, Ga.*

Surgical Treatment of Partial and Total Anomalous Pulmonary Venous Drainage. *Johann L. Ehrenhaft, Montague S. Lawrence, and Ernest O. Theilen, Iowa City, Ia.*

Evaluation of the Surgical Treatment of Patients with Coexisting Atrial Septal Defect and Pulmonary Valvular Stenosis. *Henry Swan and S. Gilbert Blount, Jr., Denver, Colo.*

High Blood Pressure

G. B. Shaw Room—9:00 A.M. to 12:30 P.M.

Chairman: **Meyer W. Friedman, San Francisco, Calif.**

Co-Chairman: **James V. Warren, Durham, N. C.**

Studies on the Natural History of Adrenal Regeneration Hypertension. *Floyd R. Skelton, New Orleans, La.*

Enhancement of Antihypertensive Activity with Chlorothiazide. *Edward D. Freis, Ilse M. Wilson, and Alvin E. Parrish, Washington, D. C.*

Occurrence of Hypertensive Toxemia in Mother-Daughter Pairs. *J. O'Neal Humphries, Baltimore, Md.*

Re-examination of the Mechanism of Arterial Hypertension in Patients with Coarctation of the Aorta. *Walter M. Kirkendall, John W. Eckstein, and James W. Culbertson, Iowa City, Ia.*

Work of Digital Vasoconstriction Produced by Infused Norepinephrine in Primary Hypertension. *Milton Mendlowitz and Nosrat N. Naftchi, New York, N. Y.*

INTERMISSION

Evidence for an Extra-Vascular T-1824 Space. *Frank A. Finnerty, Jr., Joachim H. Buchholz, and Robert L. Guillaudeu, Washington, D. C.*

Severe Arteriosclerosis Produced in the ACTH-Treated Rat. *Bernard C. Wexler and Benjamin F. Miller, Cincinnati, Ohio.*

Renal Rheoplethysmogram of the Dog. *George E. Burch and John H. Phillips, Jr., New Orleans, La.*

Synthesis of the Angiotonin Octapeptide. *Hans J. Schwarz, Merlin F. Bumpus, and Irvine H. Page, Cleveland, Ohio.*

MEDICAL MOTION PICTURES

DAILY PROGRAM

OCTOBER 25 to 28, 1957

October 25, Ruby Room **October 26-28, Old Chicago Room**

9:30 A.M. to 12:00 Noon

9:30 **William Harvey and the Circulation of the Blood** (Color, Sound)
Royal College of Physicians, Sir Henry Dale, London, England

10:15 **Open Operation for Aortic and Pulmonic Stenosis** (Color, Sound)
Henry Swan, M.D., Denver, Colo.

10:35 **Disorders of the Heart Beat** (Color, Sound)
American Heart Association, New York, N. Y.

10:55 **Tetralogy of Fallot** (Color, Sound)
John C. Jones, M.D., Los Angeles, Calif.

11:25 **Anatomic Correction of the Tetralogy of Fallot Defects under Direct Vision, Utilizing the Pump-Oxygenator** (Color, Sound)
C. Walton Lillehei, M.D., Minneapolis, Minn.

2:00 P.M. to 5:00 P.M.

2:00 **William Harvey and the Circulation of the Blood** (Color, Sound)
Royal College of Physicians, Sir Henry Dale, London, England

2:45 **Aortic Graft for Abdominal Aneurysm** (Color, Sound)
A. W. Humphries, M.D., Cleveland, Ohio

3:05 **Femoral Graft for Arteriosclerosis Obliterans** (Color, Sound)
A. W. Humphries, M.D., Cleveland, Ohio

3:25 **Movements of the Valves of the Heart and the Origin of the Heart Sounds** (Color, Combination of Silent and Sound)
H. E. Essex, M.D. and H. L. Smith, M.D., Rochester, Minn.

3:50 **Still Going Places** (Black and White, Sound)
Frederick D. Zeman, M.D. and Leo Dobrin, M.D., New York, N. Y.

4:30 **Hepato-Jugular Reflex** (Color, Sound)
J. Marion Bryant, M.D., New York, N. Y.

SCIENTIFIC EXHIBITS

Lower Exhibit Hall

Genetic Determination of Serum Cholesterol Level: Study of 201 Families. *David Adlersberg, Louis E. Schaefer, and Arthur G. Steinberg, New York, N. Y.*

Analysis of 201 families, 402 parents and their 373 children, totaling 775 individuals, selected at random from a group of employees of low-middle income. The frequency of hypercholesteremia was 17 per cent among the children who had a hypercholesteremic parent and 2 per cent among children of normocholesteremic parents. Correlation coefficients indicate that the serum cholesterol levels of fathers and mothers were unrelated, whereas the levels of the children were significantly associated with those of the parents and the levels of the siblings significantly related to each other. These data add evidence to the concept that serum cholesterol concentration at any level is genetically determined and that predisposition to atherosclerosis may be, at least in part, genetic in its nature.
(Booth I)

Use of a Sphere for the Analysis of Electrocardiac Entities in Space. *Louis Brinberg, New York, N. Y.*

Vectors are represented by points on the surface of a sphere and the method of determining these points is shown. A spatial angle equals the arc distance between two points. Normal values are demonstrated for electric axis, ventricular gradient, QRS-T angle and QRS-VG angle.
(Booth L)

Ventricular Septal Defect—Diagnosis and Surgical Treatment. *H. B. Burchell, R. O. Brandenberg, A. J. Bruwer, D. E. Donald, J. W. DuShane, J. E. Edwards, H. G. Harshbarger, J. W. Kirklin, H. J. C. Swan, and E. H. Wood, Rochester, Minn.*

It is important to recognize the varied clinical syndromes produced by ventricular septal defects now that surgical repair of these defects is being accomplished. These syndromes and their relation to the size of the ventricular septal defect and the magnitude of pulmonary resistance are illustrated and described. The pathologic anatomic features of ventricular septal defect, both as an isolated lesion and as part of the tetralogy of Fallot, are demonstrated by models. Roentgenologic, electrocardiographic and clinical features pertinent to the diagnosis of this malformation are depicted. Hemodynamic data are correlated with other observations in cases of ventricular septal defect. The technic for repair of ventricular septal defect by open cardiotomy while the patient is supported by a mechanical pump-oxygenator is shown. The results of surgical repair support the belief that operation is indicated for patients with large left-to-right shunts across ventricular septal defects.
(Booth Q)

Rapid and Reliable Screening Method for Detection of Heart Disease in Children. *Chicago Heart Association, United States Public Health Service, and Chicago Board of Health, Chicago, Ill.*

Studies using tape recording equipment modified by us have demonstrated that this method can be utilized in mass screening of school children for heart disease. This technic can record 50 children per hour with a high degree of accuracy as proven by statistical study of large numbers of recordings.
(Booth B)

Subminiature Intracardiac Manometer for Infants and Adults. *E. H. Drake, Detroit, Mich., and A. Warnick, Dearborn, Mich.*

The exhibit shows a functioning intracardiac manometer of hollow construction mounted on a No. 6 French catheter. Intracardiac manometry eliminates distortion created by pressure transmission through fluid columns. The new instrument faithfully records dynamic variations within the physiologic range. An enlarged model is presented showing construction details and representative pressure tracings are displayed.
(Booth H)

Evaluation of Arterial Reconstruction and Sympathectomy by Direct Stimulation Ergometry. *Edward A. Edwards, Boston, Mass.*

Electric stimulation of the calf muscles was employed in 48 limbs before and up to 3 years after operation to relieve ischemia. A measured average increase in power was maximal at 10 months after reconstruction and 13 months after sympathectomy. Instances of lack of improvement can be partly explained.
(Booth F)

Open Heart Surgery in Acquired Valvular Disease. *Earle B. Kay, Frederick S. Cross, and Henry A. Zimmerman, Cleveland, Ohio.*

The exhibit will deal with the indications and contraindications to open heart surgery and acquired valvular disease. The technical aspects essential to left sided cardiotomies will be emphasized. Surgical and pathological illustrations of the types of acquired valvular disease amenable to surgery will be presented as well as the morbidity factors and results. A movie illustrating many of these aspects also will be incorporated into the exhibit.
(Booth A)

Evaluation of C-Reactive Protein and SGO Transaminase in Coronary Artery Disease. *Irving G. Kroop and Nathan H. Shackman, Brooklyn, N. Y.*

The C-reactive protein test is more sensitive than the transaminase test in the diagnosis of the milder case of myocardial necrosis but cannot be used unless all extracardiac stimuli for its formation are absent. The transaminase level is not diagnostic in these cases because insufficient enzyme is released to elevate the serum concentration beyond the normal range (29 out of 45 cases).
(Booth M)

Timed Vital Capacity. *C. M. Kurtz and J. K. Curtis, Madison, Wis.*

Timed vital capacity (TVC) differentiates between restrictive and obstructive types of breathing. Hence this test is helpful in distinguishing asthmatic bronchitis and cardiac asthma. In cardiac decompensation the vital capacity (VC) is reduced and improves with establishment of compensation. A simple spirometer apparatus will demonstrate how records of VC and TVC may be made on the electrocardiograph.
(Booth C)

Anisindione—New Improved Anticoagulant. *Kurt Lange, Murray M. Mahl, Eli Perchuk, and Joseph Enzinger, New York, N. Y.*

Anisindione, an oral anticoagulant of the indandione type, elicits predictable and rather uniform effects with a given dose. Its action is prompt and sustained. A smooth curve of hypoprothrombinemia is obtained with a maintenance dose every third day. The required dosage varies very little from case to case. To produce undesirably low prothrombin activity excessively large doses of anisindione are required.
(Booth P)

Influence of Cardiopulmonary Bypass Procedures on Cardiac Contractility and Sympathoadrenal Function. *Wm. H. Lee, Jr., Thomas D. Darby, Eugene F. Woods, J. D. Ashmore, James A. Richardson, and Edward F. Parker, Charleston, S. C.*

Direct measurements of changes in the force of contraction of the ventricular musculature were used for the early detection of disturbances in cardiac function secondary to cardiopulmonary bypass procedures. Evidence is presented that serious deficiencies in cardiac contractility may occur when the electrocardiogram, arterial pressure, etc. are essentially unchanged. Participation of the sympathoadrenal system has been evaluated by measuring plasma concentrations of epinephrine and arterenol.
(Booth G)

Controlled Study on the Prevention of Streptococcal Infection and Rheumatic Fever with Penicillin. *Benedict F. Massell, Samuel L. Stancer, Joseph M. Miller, John A. Vecchiolla, Sidney Brodie, and Eliot Young, Boston, Mass.*

The relative advantages and disadvantages of oral buffered penicillin G, oral penicillin V, and intramuscular benzathine penicillin G for preventing streptococcal respiratory infection (and rheumatic fever) are demonstrated. Effectiveness is measured by comparing the incidence of streptococcal infection among rheumatic subjects, given penicillin, and among their siblings, not given penicillin.
(Booth J)

Pulmonary Hypertensive Cardiovascular Disease. *Thomas W. Mattingly, Loren F. Parmley, Jr., and Robert J. Hall, Washington, D. C.*

The exhibit presents a classification of pulmonary hyperentsive cardiovascular disease and depicts the incidence as encountered during a 6-year clinical study, including over 500 right heart catheterizations. The clinical, hemodynamic, and pathologic features of the primary and secondary forms of the disease are demonstrated with emphasis on the distinguishing features of each. Current ideas as to pathogenesis and approaches to therapy are also presented.
(Booth D)

Encouraging News about Strokes. *National Heart Institute and Heart Disease Control Program, Public Health Service, Bethesda, Md.*

Hope and help for people who have suffered strokes is the keynote of a Public Health Service exhibit, poster, and booklet designed for use by physicians and other professional persons to promote better understanding of cerebral vascular disease and strokes among patients, their families, and the general public.
(Booth S)

Strokes Caused by Diseases of the Heart and Aorta. *T. W. Parkin, C. H. Millikan, G. P. Sayre, and J. E. Edwards, Rochester, Minn.*

Considerable interest has developed recently concerning the problem of strokes. In most instances, strokes are associated with primary disease of cerebral arteries, but they may be caused at times by certain diseases of the heart or aorta. Such strokes may result from (1) cerebral ischemia caused by decreased cardiac output, (2) cerebral embolism or (3) cerebral hemorrhage. This exhibit portrays with models and photographs the important diseases of the heart and aorta that may produce strokes. The chief clinical manifestations of strokes occurring as complications of cardiac diseases and the underlying pathologic changes in the brain are illustrated.
(Booth N)

Prevention of Rheumatic Fever. *Rheumatic Fever Prevention Sub-Committee, Chicago Heart Association, Chicago, Ill.*

The exhibit will emphasize the management of streptococcal infections in private practice, including

ive demonstrations of practical throat-culturing echnics. Material on primary, as well as secondary, revention will be available. A portable laboratory or the purpose of taking throat cultures on the spot ill be a part of the exhibit.
(Booth T)

Disposable Oxygenator with Low Priming Volume. *Peter F. Salisbury, Los Angeles, Calif.*
A plastic disposable oxygenator will be shown which can arterialize 1,200 to 1,500 ml. blood per minute and which requires only 200 to 300 ml. priming blood. It is primarily intended as an auxiliary circulation in patients with intractable heart failure, but can also be used for open heart surgery.
(Booth O)

Left Transventricular Approach to the Aortic and Mitral Valves and to the Interventricular Septum. *Victor P. Satinsky, Eugene V. Kompaniez, Robert Kuhn, and Richard N. Baum, Los Angeles, Calif.*
After bypassing the heart and lungs by means of a pump-oxygenator, easy access to the interventricular septum, the annulus of the aortic valve and the leaflets of the mitral valve may be obtained. Either retrograde coronary artery perfusion or induced cardiac arrest may be employed as an adjunct to the procedure.
(Booth R)

Timed Vectorcardiogram. *Ronald H. Selvester and Donald E. Griggs, Los Angeles, Calif.*
The spatial vectorcardiogram graphically portrays vector forces. However, P, QRS, and T are often superimposed; time relationships are hard to evaluate; rate, PR, and QT intervals are not recorded. Electrocardiograms depict more clearly time relationships of cardiac cycle. The timed vectorcardiogram combines advantages of each into simplified graphic method.
(Booth K)

American Heart Association
Information booth and display of materials for the physician.
(Booth E)

TECHNICAL EXHIBITS

Main Exhibit Hall

Arlington Medical Company, Arlington Heights, Ill. (Booth 22).

Baxter Laboratories, Inc., Morton Grove, Ill. (Booth 65), *presents Sera-Vac—the only blood bottle with the internal pilot tube—prevents errors, saves time. Transfuso-Vac for better platelet preservation. Plexitron Sets for simpler blood collection and transfusion. The R-48 Blood Administration Set provides for both Gravity blood transfusion and safe Pressure transfusion procedures.*

Beck-Lee Corporation, Chicago, Ill. (Booth 14). *World's largest exclusive manufacturer of EKG's, will display their Cardi-all Direct Writing EKG. This instrument features full-scale performance, extreme simplicity of operation, life-time standardization, light-weight portability, and rugged construction. Cardi-all is housed in a solid-mahogany cabinet which contributes to its outstanding modern appearance.*

Bowen & Company, Inc., Bethesda, Md. (Booth 64). *Actual demonstrations of our accurately Calibrated Ballistocardiograph, Smith-Perls Model, will be presented. Additional products displayed will be: Welsh Self-Retaining Electrodes, QU Calculator for determining the QTc or the QT Ratio, Bowen Liquid Dispenser for alcohol and other cleansing liquids. Newest item will be the Krasno-Graybiel Metal Plastrodes: a metal and plaster electrode requiring no electrode paste (jelly).*

Brewer & Company, Inc., Worcester, Mass. (Booth 17). *This exhibit consists of specialties centering around Thesodate, the original enteric-coated tablet of theobromine sodium acetate, and includes our newer products: R-S-Thesodate, which is a combination of Thesodate and Rauwolfia serpentina whole powdered root; and Rauwolfia serpentina tablets 50 and 100 mg. Also featured are: Amchlor, enteric-coated, 1 Gm. tablets of ammonium chloride; Enkide, enteric-coated tablets of potassium iodide; Gel-Ets, the newest mode in oral vitamin therapy; and Soduxin (sodium succinate-Brewer) ampuls. Literature will be available on Injectable Quinidine Hydrochloride (original injectable quinidine product on the American market for both intravenous and intramuscular use), and Sus-Phrine (aqueous suspension of epinephrine 1:200—Brewer) for subcutaneous injection in the treatment of bronchial asthma.*

Burdick Corporation, Milton, Wis. (Booth 35), *will display their latest models of electrocardiographic equipment. Burdick customers are invited to stop by their booth to make or renew acquaintance. Those not familiar with the Burdick Electrocardiograph are invited to see it in operation. Members of their sales and engineering staff will be there to greet you.*

Burroughs Wellcome & Company (U. S. A.) Inc. Tuckahoe, N. Y. (Booth 71). *The extensive research facilities of B. W. & Co., both here and in other countries, are directed to the development of improved therapeutic agents and technics. Through such research they have made notable advances related to leukemia, malaria, diabetes, and diseases of the autonomic nervous system, and to antibiotic, muscle-relaxant, antihistaminic, and antinauseant drugs. An informed staff at their booth will welcome the opportunity to discuss their products and latest developments with you.*

Cambridge Instrument Company, Inc., New York, N. Y. (Booths 45 and 46). *The Cambridge Audio-Visual Heart Sound Recorder; the well-known Cambridge "Simpli-Scribe" Model Direct-Writing Portable Electrocardiograph and the Cambridge Standard String Galvanometer Electrocardiograph, both in the "Simpli-Trol" Portable and the Mobile Model Electrocardiograph-Stethograph with Pulse Recorder, will be displayed. Also other important Cambridge instruments, including the Operating Room Cardioscope, Educational Cardioscope, Multi-Channel Direct-Writing Recorder, Catheterization Monitor-Recorder, Electrokymograph, Plethysmograph, pH Meters and Respiratory Gas Analysers. The Cambridge Engineers in attendance will be glad to give you complete information on these instruments.*

Carnation Company, Los Angeles, Calif. (Booth 49) *welcomes friends of long standing as well as new members. At their booth, a refreshing drink of Carnation Instant Nonfat Milk will be served. Carnation representatives will be pleased to discuss with you the physician-researched material for use in your practices as a service of their company.*

Coca-Cola Company, Atlanta, Ga. *Ice-cold Coca-Cola will be served through the courtesy and cooperation of The Coca-Cola Company.*

Colson Corporation, Elyria, Ohio (Booth 59). *The Colson Densitometer used in the determination of cardiac output by the dye-dilution method will be demonstrated on a model of the circulation. Actual output curves will be recorded, using the newly developed constant velocity hypodermic syringe actuator to draw fluid through the cuvette. Also in operation will be Colson's Automatic Sphygmomanometer, periodically recording diastolic and systolic pressure on an unattended subject.*

Dallons Laboratories, Inc., Los Angeles, Calif. (Booth 9), *will display their new 1958 Cardioscope and demonstrate its operation for continuous monitoring of cardiac potentials during surgery. The Dallons CP-3-6 Cardiophone will also be demonstrated. The Cardiophone produces clear and distinct sound translation of the heart muscle potentials. Any deviation from normal heart rhythm or electric potentials is immediately discernible. The Cardiac Defibrillator and Cardiac Pacer will also be shown. Competent factory representatives will be on hand to answer your questions and you are cordially invited to visit their booth.*

Darwin Laboratories, Los Angeles, Calif. (Booth 2). *Lipo-Hepin 200; sodium heparin U.S.P. in purified form allowing only 1 or 2 injections per day for 24-hour anticoagulant effect, regardless of patient weight. Ready to use, no prewarming, convenient, economical and effective. Dar-Zyme: purified trypsin with antibiotic in ointment form for topical proteolytic digestion of necrotic tissue. Ready to use, economical, convenient and effective. Adrenalex-Geriatric: Hormone (estrogentestosteron), vitamin and hemotopoietic combination capsule for use in treatment and prevention of certain geriatric problems.*

Davies, Rose & Company, Ltd., Boston, Mass. (Booth 68). *A cordial invitation is extended to the members to visit their booth. Although most physicians need no introduction to their outstanding cardiac therapies—Pil. Digitalis and Tablets Quinidine Sulfate (Natural)—our representatives, Messrs. H. V. Orne and W. Earle Purinton, will be present to welcome you and to explain the dependability of their laboratory productions.*

F. A. Davis Company Medical Publishers, Philadelphia, Pa. (Booth 67). *The new Looseleaf Edition of Stroud & Stroud:* Cardiovascular Disease *will be shown for the first time at the American Heart Association meeting. Sixty outstanding authorities in cardiology have contributed new and revised chapters in the foremost postgraduate presentation of Cardiology available today. See also Simon:* Chest X-Ray Diagnosis *and a preview of Glasser:* Peripheral Vascular Surgery.

Electrodyne Company, Inc., Norwood, Mass. (Booth 42). *On display will be the latest instruments for closed chest detection and treatment of cardiac arrest and ventricular fibrillation. Featured will be the Electrodyne PM-65 with Electrocardioscope, which reliably monitors cardiac activity and automatically provides effective external stimulation of the dormant heart at the very onset of cardiac arrest. The PM-65 combines the popular Cardiac Monitor and the well-documented Electrodyne Cardiac Pacemaker into 1 versatile unit.*

Electronics For Medicine, Inc., White Plains, N. Y. (Booth 47). *A new 8-channel research recorder provides both scalar and loop tracings with an improved cathode ray camera. Cardiovascular and respiratory pressures, electrocardiogram, electroencephalogram, phonocardiogram and oxygen saturation can be recorded along with polarographic measurements, integrals, derivatives, and pressure gradients. The Cardiology Teaching Aid permits simultaneous tape recording for phonocardiogram and electrocardiogram or pulse wave, with visual and aural examination and permanent tracings.*

Encyclopaedia Britannica, Chicago, Ill. (Booth 21). Encyclopaedia Britannica *proudly announces the release of a brand new edition. Thirteen years of intensive editorial effort, representing an investment of more than five million dollars is reflected in this New Edition. You are cordially invited to inspect the finest* Britannica *ever published and to avail yourselves of the most sensational offer savings-wise ever made.*

Evron Company, Inc., Chicago, Ill. (Booth 32). *Pentritol Tempules for continuous 24-hour treatment of angina pectoris are presented. The significance of the 12 hours of coronary vasodilation produced by each 30 mg. capsule of PETN is substantiated by actual use. Since its introduction over 2 years ago, Pentritol has gained the support of clinical studies and office experience to establish its effectiveness. Prescribing 1 Tempule every 12 hours has been consistently valuable in controlling anginal spasms. Professional Representatives available to offer service, samples and literature.*

C. B. Fleet Company, Inc., Lynchburg, Va. (Booth 69). *Fleet will introduce Clysmathane, a coronary vasodilator and bronchodilator. Administration is by a new and simple method.*

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Yonkers, N. Y. (Booth 62). *The Geigy exhibit will feature Preludin—the new chemically different appetite suppressant noted for its absence of side actions. Also on display will be Butazolidin—potent nonhormonal antiarthritic; new Sterosan hydrocortisone ointment—anti-inflammatory, bacteriostat and fungistat, and other well-known Geigy products.*

Grass Instrument Company, Quincy, Mass. (Booth 7). *Direct Recording Polygraph Model, 5 to be exhibited. This versatile instrument is designed to measure neurologic and circulatory functions, including EEG, EKG, EMG, respiration, pressure, plethysmography O_2, CO_2, PGR. The application is in the operating room, clinic, laboratory, and class room.*

Gray Pharmaceutical Company, Inc., Newton, Mass. (Booth 23). *Atheroxin, the only corn oil-pyridoxine emulsion for the reduction of cholesterol will be exhibited. Atheroxin combines the cholesterol lowering factors of corn oil with pyridoxine hydro-*

chloride, a singularly effective agent for the utilization of essential unsaturated fatty acids. Atheroxin may be used to reduce serum cholesterol in patients with coronary artery disease and other conditions which exhibit an elevated cholesterol.

Grune & Stratton, Inc., Medical Publishers, New York, N. Y. (Booths 40 and 41). *Grune & Stratton invites you to examine* Circulation *and* Circulation Research *with our Mr. Frank Kurzer, and also such recent books as: Askey:* Arterial Embolism; *Alpers:* Dizziness; *Gordon:* Clinical Cardiopulmonary Physiology; *Redisch:* Peripheral Circulation in Health and Disease; *Scherf and Boyd:* Cardiovascular Diseases, *third revised edition; Sigler:* The Electrocardiogram, *second revised edition; Kossmann:* Progress In Electrocardiography, *and other valuable works for the practicing physician in internal medicine.*

Paul B. Hoeber, Inc., New York, N. Y. (Booth 3). *Here you will be able to examine 4 new and important books published this year: Plotz'* Coronary Heart Disease, *Gardberg's* Clinical Electrocardiology, *Naclerio's* Bronchopulmonary Diseases, *and Bayley's* Biophysical Principles of Electrocardiography, *just coming off press. All books on the Hoeber-Harper list will be available, and you are invited to browse at leisure.*

Industrial Acoustics Company, Inc., New York, N. Y. (Booth 26). *will display material showing the use of an I.A.C. Series "1200" soundproof room for research of heart sounds and auscultation. These rooms are designed and engineered to provide the ultimate in acoustical performance. The features which make these rooms unique in their field will be pointed out.*

Lea & Febiger, Philadelphia, Pa. (Booth 1), *welcomes you to their booth where you can examine such books as Katz and Pick*—Clinical Electrocardiography; *Master, Moser and Jaffe*—Cardiac Emergencies and Heart Failure; *Goldberger*—Heart Disease; *Burch and Winsor*—Primer of Electrocardiography; *Burch*—Primer of Cardiology; *Goldberger*—Unipolar Lead Electrocardiography; *Pratt*—Cardiovascular (Artery and Vein) Surgery; *and many others.*

Lederle Laboratories, Division of American Cyanamid Company, Pearl River, N. Y. (Booth 15).

Thos. Leeming & Company, Inc., New York, N. Y. (Booth 36). *The use of Metamine (triethanolamine trinitrate biphosphate) in the prevention of angina pectoris will be presented. The b.i.d. dosage form of this drug, Metamine Sustained, will be featured, and physicians who are not familiar with this unique cardiac nitrate are urged to visit our booth, where comprehensive literature will be available.*

Eli Lilly and Company, Indianapolis, Ind (Booths 5 and 6). *You are cordially invited to visit the Lilly exhibit. Sales people in attendance welcome your questions about Lilly products and recent therapeutic developments.*

Macmillan Company, New York, N. Y. (Booth 44). *The Macmillan Company will have on display some well-established, as well as several new, titles in the cardiology field. Of special interest will be Briskie:* Cardio-Charting: Universal Method of Recording Heart Auscultation, *and Keith-Rowe-Vlad:* Heart Disease in Infancy and Childhood.

Maico Company, Inc., Minneapolis, Minn. (Booth 52), *will show their amplifying electronic stethoscope, the Maico Stethetron. By means of filters this instrument will permit one to concentrate on the low-pitched heart murmurs while screening out the higher-pitched tones. Experienced personnel will be on hand to give you a demonstration.*

Mark Company, Randolph, Mass. (Booth 37). *Introducing for the first time in this country, universally accepted famous Schwarzer Electrocardiographs, employing from 1 to 16 channels. Also, all stainless steel, completely autoclavable, Cooley Mechanical Heart-Lung and Clowes Membrane Oxygenator, in addition to explosion-proof Heart Defibrillator, and Gibbon-type Mark GK Mechanical Heart-Lung Apparatus.*

Merck Sharp & Dohme, Division of Merck & Company, Inc., Philadelphia, Pa. (Booth 34). *Their exhibit highlights steroid therapy featuring new adrenal cortical steroid preparations—Meprolone, Hydeltra-T.B.A., and Neo-Hydeltrasol. New antibacterial agents of clinical significance are also featured. Technically trained personnel will be present to discuss these and other subjects of clinical interest.*

C. V. Mosby Company, St. Louis, Mo. (Booth 11). *You are cordially invited to visit their booth, where you will find displayed the following new books and new editions. Sodi-Pallares* New Bases of Electrocardiography, *Myers* Interpretation of the Unipolar Electrocardiogram, *Meakins* Practice of Medicine, *Bard* Medical Physiology, *Anderson* Pathology, *Lisser-Escamilla* Atlas of Clinical Endocrinology, *and Williamson* Practical Use of Office Laboratory and X-Ray (Including the Electrocardiograph).

Nepera Laboratories Division, Morris Plains, N. J. (Booth 16). *Their exhibit features a new xanthine drug, Choledyl, which has proven highly effective and well tolerated when used orally as a prophylactic agent in chronic emphysema and bronchial asthma. Its mild diuretic action makes it useful as an oral nonmercurial diuretic in the treatment of congestive heart failure. The representatives at their booth welcome inquiries regarding this new and unique agent, and*

are prepared to discuss a recent controlled study demonstrating the effectiveness of Choledyl in preventing the recurrence of anginal attacks.

North American Philips Company, Inc., New York, N. Y. (Booth 12). *Reflecting the ever-increasing interest in this comparatively new technic, their display will consist of the 5" Philips Image Intensifier with 3 separate viewing systems; a mirror viewer, cineradiographic hook-up and a closed circuit television execution, the 11" Philips Image Intensifier designed primarily for cineradiographic studies.*

Pet Milk Company, St. Louis, Mo. (Booth 60). *They will be pleased to have you stop and taste the "fresh milk flavor" of Instant "Pet" Nonfat Dry Milk. Their representatives will be on hand to serve you and discuss the use of Instant "Pet" Nonfat Dry Milk in special diets.*

Raytheon Manufacturing Company, Waltham, Mass. (Booth 50).

Riker Laboratories, Inc., Los Angeles, Calif. (Booth 43). *Their exhibit features its list of pioneering firsts: Rauwiloid (alseroxylon) and its combinations in the management of hypertension; Pentoxylon in angina pectoris; the new highly effective skeletal muscle relaxant, Disipal, for relief of muscular spasm in backache, injuries, arthralgias and Parkinsonism. Also featured is Medihaler-Epi and Medihaler-Iso, measured-dose aerosol nebulization for effective asthma control.*

Sanborn Company, Waltham, Mass. (Booths 29 and 30). *Visitors at their booth will have full opportunity to see and have demonstrated our continually expanding line of equipment for biophysical diagnosis, teaching and research. Instrumentation to be shown or described will include single and multi-channel recording systems—direct-writing, photographic and tape; supplementary oscilloscopes; and physiologic transducers of several types. Workers in the cardiovascular and other research fields should not miss the opportunity to examine this varied equipment, and to discuss with our engineers its applicability to their investigative problems.*

Sandoz Pharmaceuticals Division, Hanover, N. J. (Booth 66). *You are cordially invited to visit their display: Acylanid has all the advantages of digitoxin but has the safety of the whole leaf digitalis. Cedilanid pure glycoside (lanatoside C) of digitalis lanata with quick onset of action, quick excretion, low toxicity useful for i. v. administration in cardiac emergencies. Their representatives will gladly answer questions about this and other Sandoz products.*

Instant Sanka Coffee, White Plains, N. Y. (Booths 72 and 73). *You are invited to stop by their booths for a cup of Instant Sanka, a hearty coffee. Sanka is pure coffee, 97 per cent caffein-free . . . there isn't a jitter in a jarful. Do try Instant Sanka, and while at their booth, register for professional samples and booklets.*

W. B. Saunders Company, Philadelphia, Pa. (Booth 63). *Current Saunders titles of special interest to physicians in heart work include: Nadas:* Pediatric Cardiology; *Rodriguez:* An Atlas of Cardiac Surgery; *and Friedberg:* Diseases of the Heart.

Schering Corporation, Bloomfield, N. J. (Booth 31). *Members of the Association and guests are cordially invited to visit the Schering exhibit where new therapeutic developments will be featured. Their representatives will be present to welcome you and to discuss with you the various products they manufacture.*

Schieffelin & Company, New York, N. Y. (Booth 33).

G. D. Searle & Company, Chicago, Ill. (Booth 8). *You are cordially invited to visit their booth where representatives will be happy to answer any questions regarding their various products of research. Featured will be Nilevar, the new anabolic agent; Rolicton, the new safe, non-mercurial oral diuretic; Vallestril, the new synthetic estrogen with extremely low incidence of side reactions; Banthine and Pro-Banthine, the standards in anti-cholinergic therapy; and Dramamine, for the prevention and treatment of motion sickness and other nauseas.*

Sherman Laboratories, Detroit, Mich. (Booth 56). *When therapeutic theophylline blood-levels are achieved, the myocardium is strengthened, bronchioles and peripheral blood vessels are relaxed, venous pressure is lowered, circulation time is shortened and coronary and pulmonary circulations are increased. Hitherto, these effects were reliably available only with parenteral therapy. Now, these clinically valuable properties of theophylline are dependably secured by the oral route—with Elixophyllin.*

E. R. Squibb & Sons, New York, N. Y. (Booth 13), *has long been a leader in development of new therapeutic agents for prevention and treatment of disease. The results of their diligent research are available to the medical profession in new products or improvements in products already marked. At their booth, they will be pleased to present up-to-date information on these advances for your consideration.*

Statham Laboratories, Inc., Los Angeles, Calif. (Booth 53). *Four types of Statham unbonded strain gage manometers intended especially for biologic measurements will be displayed by experienced engineering personnel. These 4 models of Statham pressure transducers have found wide acceptance in*

the field of cardiac catheterization because of their inherent stability, excellent dynamic response and simplicity of operation.

R. J. Strasenburgh Company, Rochester, N. Y. (Booth 48). *New Biphetamine, providing a more satisfactory means of controlling body weight where indicated, is featured. Clinicians report an average weight loss characteristic of 2 to 3 lbs. per week in nearly all cases of obesity due to excessive eating. Predictable sustained ionic release assures 10- to 12-hour appetite suppression without discomfort or disturbance of normal sleeping habits. For details, visit their booth.*

Charles C Thomas, Publisher, Springfield, Ill. (Booth 70). *Some of the books they will display for the first time are: Edwards*—Plastic Arterial Grafts; *Gasul, et al.*—Angiocardiography in the Diagnosis of the Cyanotic Types of Congenital Malformations of the Heart; *Lamb*—Electrocardiography and Vectorcardiography; *Rinzler*—Clinical Aspects of Arteriosclerosis; *Rabin*—Roentgenology of the Chest *sponsored by the American College of Chest Physicians; Schroeder*—Mechanisms of Hypertension.

U. S. Vitamin Corporation, New York, N. Y. (Booth 39). *New—on display—Arlidin, the safe vasodilator drug with 3 unique pharmacologic actions: (1) dilates predominantly small blood vessels of skeletal muscle, (2) increases cardiac output without significant increase in pulse rate, (3) promotes greater circulating blood volume. Thus, Arlidin (Nylidrin HCl. NNR) is indicated in treating intermittent claudication in arteriosclerosis obliterans, thromboangiitis obliterans, and diabetic vascular disease; also effective in Raynaud's Syndrome and ischemic ulcers. Professional samples and literature distributed also on their complete line of nutritional and pharmaceutical specialties.*

Varick Pharmacal Company, Inc., Hicksville, N. Y. (Booth 57). *Digitaline Nativelle Intramuscular, the only parenteral digitoxin designed specifically for intramuscular injection will be described. Indicated when the oral route is unavailable, Digitaline Nativelle Intramuscular exerts the identical response of oral or intravenous Digitaline Nativelle, both as to speed of action and therapeutic effect. Clinical supplies for evaluation will be available on request.*

Walker Laboratories, Inc., Mt. Vernon, N. Y. (Booth 10). *At their booth, the feature product being exhibited is: Hedulin (PID), the oral anticoagulant of choice Ref. 1. Breneman, C. M. et al: Am. Heart J., July '55. Full details pertaining to the drug and reprints of all medical papers are available in complete portfolio form.*

Warner-Chilcott Laboratories, Morris Plains, N. J. (Booth 25). *Peritrate—Warner-Chilcott Laboratories feature Peritrate Sustained Action, a new dosage form of the long-acting coronary vasodilator, Peritrate. For the first time the angina patient is provided with around-the-clock protection against attack. Peritrate is effective in 4 out of 5 cases. Improved E. K. G. readings, and increased exercise tolerance offer objective evidence of Peritrate's effectiveness in angina.*

Waters Corporation, Rochester, Minn. (Booth 38), *will demonstrate its self-developing photokymograph recorder in combination with matching "modular control" system for simultaneous recording of multiple cardiopulmonary phenomena monitored by a 17-inch screen oscilloscope. Also featured will be a new, stable nitrogen gas analyzer, oximeter, cardiotachometer, and a thermistor offering extra sensitive, fast probes.*

Winthrop Laboratories, New York, N.Y. (Booth 20). *Isuprel (Ampuls and Glossets) for heart block, Adams-Stokes syndrome, cardiac standstill, carotid sinus hypersensitivity, and cardiac arrhythmias. In the management of these conditions, Isuprel has the unique advantage of stimulating and stabilizing the active ventricular pacemaker of the heart without inciting lower potential ventricular foci. Therefore, Isuprel in contrast to epinephrine, does not predispose the heart to ventricular fibrillation or tachycardia.*

Wyeth Laboratories, Philadelphia, Pa. (Booths 27 and 28), *will feature: Bicillin Injection (benzathine penicillin G) long-acting penicillin compound, valuable in rheumatic fever prophylaxis. Pen-Vee-Oral (penicillin V) new acid-stable oral penicillin which produces high blood levels. Sparine (promazine hydrochloride) potent ataractic drug, indicated in management of acutely agitated patients. Equanil (meprobamate) unique antianxiety agent with marked muscle-relaxing properties. Ansolysen (pentolinium tartrate) effective oral ganglionic blocking agent for management of hypertension. Thiomerin Sodium (mercaptomerin sodium) Injection and Rectal Suppositories, mercurial diuretic, virtually free of local or systemic toxicity.*

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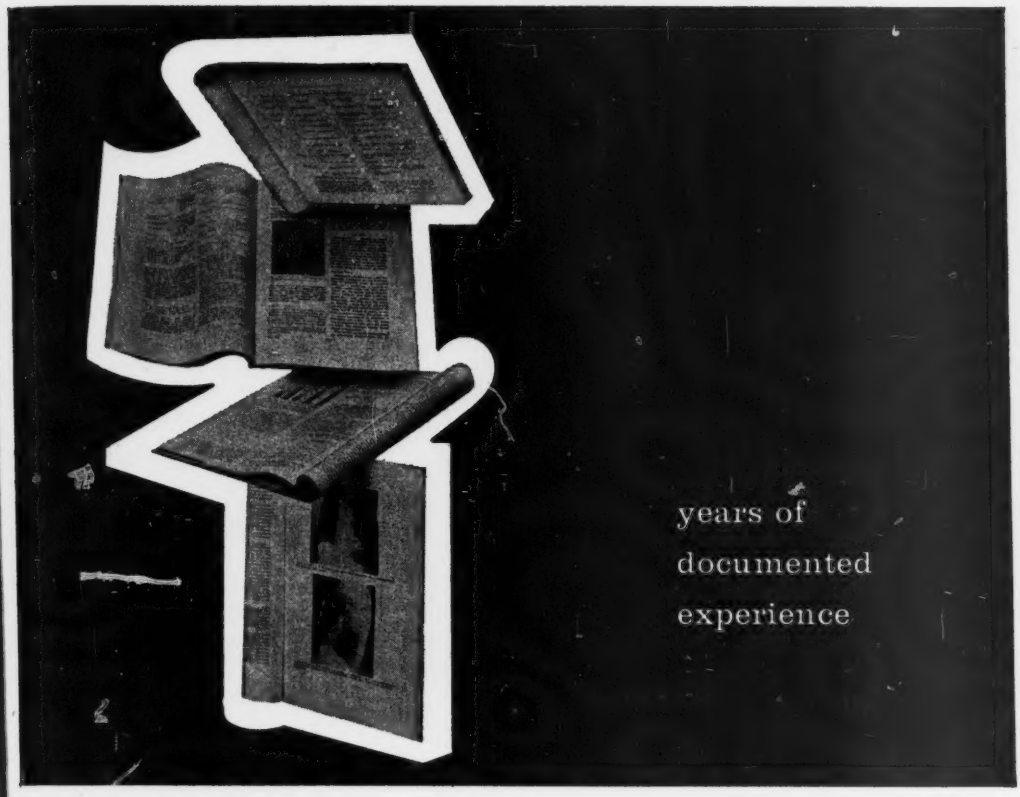

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Circulation

OCTOBER 1957
VOL. XVI NO. 4

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

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